Preliminary Transcript

HEARING ON SAFE AND AFFORDABLE BIOTECH DRUGS: THE NEED FOR A GENERIC PATHWAY

Monday, March 26, 2007

House of Representatives,

Committee on Oversight and

Government Reform,

Washington, D.C.

Committee Hearings

of the

U.S. HOUSE OF REPRESENTATIVES

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The subcommittee met, pursuant to call, at 10:00 a.m. in room 2154, Rayburn House Office Building, the Honorable Henry A. Waxman [chairman of the committee] presiding.

Present: Representatives Waxman, Kucinich, Davis of Illinois, Yarmuth, Norton, Van Hollen, Hodes, Welch, Davis of Virginia, Burton, Issa, Bilbray, and Sali.

Staff Present: Phil Barnett, Staff Director and Chief Counsel; Kristin Amerling, General Counsel; Karen Nelson, Health Policy Director; Karen Lightfoot, Communications Director and Senior Policy Advisor; Andy Schneider, Chief Health Counsel; Sarah Despres, Senior Health Counsel; Ann

Witt, Health Counsel; Robin Appleberry, Counsel; Earley Green, Chief Clerk; Teresa Coufal, Deputy Clerk; Caren Auchman, Press Assistant; Zhongrui ''JR'' Deng, Chief Information Officer; Leneal Scott, Information Systems Manager; Robin Pam, Staff Assistant; Rachel Sher, Counsel; David Marin, Minority Staff Director; Larry Halloran, Minority Deputy Staff Director; Jennifer Safavian, Minority Chief Counsel for Oversight and Investigations; Susie Schulte, Minority Senior Professional Staff Member; Kristina Husar, Minority Professional Staff Member; Patrick Lyden, Minority Parliamentarian and Member Services Coordinator; Brian McNicoll, Minority Communications Director; and Benjamin Chance, Minority Clerk.

Chairman WAXMAN. The meeting of the Committee will please come to order.

More than 20 years ago the Congress enacted the Hatch-Waxman Act. That law has taught us three things: genetic drugs are good for patients, both medically and financially; with a little help, the market works, generic competition lowers drug prices; and generic competition does not bankrupt the drug name drug industry or slow innovation.

Maybe some big drug makers still dispute these lessons, but no one else does. But there is still no generic competition for one of the fastest-growing and most expensive categories of drugs, biologicals, those drugs produced from living cell cultures rather than from chemical synthesis.

Some of these drugs are near miracles for people with cancer, metabolic diseases, and immune disorders. They can stop disability and, in some cases, save life. People need them. But some of these drugs cost each patient tens of thousands of dollars a year. Some can cost hundreds of thousands per year. Many people cannot get access to these near miracles, and even when people can get them the prices drive up the cost of Medicare, Medicaid, and health insurance overall.

Why isn't the market helping? It is not because of the patent system that biologicals are protected from the competition that might lower prices. Biologicals, like other

drugs, do enjoy patent protection. This allows manufacturers to enjoy a monopoly period during which they can get a significant return on their investments. But patents, or many of them, have already expired, and other patents are just about to expire.

And it is not the science of these drugs that protects them from competition. The technology is already here to make a safe and effective copy of some biotech drugs. Moreover, the technology is getting better every year, and we can make progress even faster if we allow companies to use it to make generics.

Instead, the monopoly on each of these drugs is perpetuated by the lack of a clear pathway for FDA to approve competing versions.

The Hatch-Waxman Act does not reach most of them. This costs all of us--taxpayers, insurance premium payers, and patients--billions of dollars. It also means that some very sick people simply cannot get the drugs they need.

I know that the science of these drugs is not simple. I take the questions of research, safety, and efficacy very seriously. The only way we can succeed in establishing robust competition for biotech drugs is with drugs the doctors and patients know they can count on, so we need to be sure that the FDA has the discretion to require the studies that are needed to establish that a copy of a biotech drug is

equivalent to the brand name drug in safety and effectiveness. That is one of the things we hope to learn more about today.

But the big brand name companies have gone beyond legitimate concern and have thrown up a defensive smoke screen around biologicals. They say there will be problems of safety, decreased innovation, and limited savings. When discussing creating generic competition, they say things like--and I am going to quote this--''such action may also save consumers a few dollars here and there, although that is by no means assured, but whatever short-term savings may be achieved will come at an enormous long-term cost to the public. Focusing solely upon short-term, lower prices, a cheap drugs policy will inevitably reduce research and hinder our public health efforts.''

Well, these arguments have a familiar ring to them. That is because the words I just read were the formal testimony that the Pharmaceutical Manufacturers Association gave to the House in 1983 when they were opposing Hatch-Waxman, and now manufacturers are using these same arguments again. But they were wrong then. Hatch-Waxman has saved patients billions of dollars and dramatically improved their access to drugs, and Hatch-Waxman did not reduce research or hinder public health.

And they are wrong now. A new path for FDA to approve

generic biologicals will save patients billions in the future and will improve access to treatments and cures, and a new path will improve competition, while preserving the market's strong incentive for research.

For the sake of patients, their families, public and private health insurance, and taxpayers, we must find a way to introduce competition to this market. When a patent expires, we owe it to consumers to find a way through competition to lower prices and still deliver a safe and effective product. When a patient expires, they no longer need the product, so the price will make no difference.

I look forward to the testimony of the witnesses today and learning more about the scope of the problem, the science, and the potential solutions.

[Prepared statement of Chairman Waxman follows:]

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Chairman WAXMAN. Mr. Davis?

Mr. DAVIS OF VIRGINIA. Thank you, Mr. Chairman, for holding today's hearing to consider the implications of creating a regulatory pathway for approval of follow-on biologics. It is a very important subject, and certainly your leadership is appreciated and worthy of this Committee's consideration.

Mr. Chairman, you have long been a leader in improving access to pharmaceutical drugs. Indeed, there is near universal agreement that the Hatch-Waxman Act has been extremely effective in allowing generic drugs to come to market and compete with brand name drugs. This competition has benefitted countless citizens, as well as the Federal Government, by using natural market economics to bring down the price of prescription medicine. You are to be commended for your leadership in improving access to these life-saving medications.

It is my understanding you have recently introduced legislation that would, in fact, create a regulatory pathway for the FDA to approve follow-on biologics. We have been reviewing the legislation with interest, and we expect it will inform today's discussion.

I look forward to exploring your proposal further. For now, let me just offer a few preliminary thoughts on this very complex subject.

The first principle guiding this effort should be to foster innovation and the discovery of new cures. After all, there is no new therapeutic, by definition there can be no follow-on. Accordingly, we need to protect the intellectual property of innovative firms. Given the high cost of research, development, manufacturing, and regulatory approvals, IP protections are clearly a critical factor for biotech startups when they are securing venture capital and pursuing partnerships with larger firms.

Today we will hear from economist Henry Grabowski, who will explain that increased patent uncertainty and IP litigation would have a significant negative effect on capital market decisions for emerging private and public biotech firms. He will explain that if the Federal Government either weakens patent protections or increases the chance of litigation there will likely be a corresponding decrease in investment, and therefore less research and development of biologics. It would be tragic if legislation intended to increase access to medicine would have the unintended result of stifling innovation, preventing the discovery of cures of presently terminal diseases.

I hope you would agree with me, Mr. Chairman, about the importance of fostering a vibrant and innovative culture where we encourage our brightest minds and daring entrepreneurs to do the research, provide the investment so

that we may some day discover the cure for cancer or Lou Gehrig's disease.

Reflecting on the Hatch-Waxman Act, you got it right when you recognized the importance of balancing the twin goals of bringing generic drugs to market while at the same time leaving intact the financial incentive for research and development.

One of the keys to this successful balance in that legislation was the guarantee of five years of market exclusivity for innovative companies. Incidentally, European Union regulators currently provide ten years of market exclusivity for European drugs for innovative drugs. Some amount of market exclusivity for the innovator is necessary under any regulatory pathway for follow-on biologics.

The second imperative is to provide a mechanism so the FDA is able to guarantee the safety and efficacy of follow-on biologics. To do so we have to recognize the fundamental differences between biologics and chemical-based pharmaceuticals. What has proven to be successful in the case of traditional drugs is not necessary transferrable to the science of biologics. For instance, it is currently possible to know the complete character of a small molecule drug. This knowledge enables the FDA to approve generic drugs with the same characteristics as the innovator drug without requiring generic companies to test and prove the

drug's efficacy and safety again. However, current science has not advanced sufficiently to give us the same confidence that a follow-on biologic is identical to a previously approved biologic based on molecular structure, alone.

Unlike traditional drugs, which are chemically based, biologics are made from living organisms. Even minor variations in manufacturing processes can have a significant impact on the final character and consistency of the biologic and its effect on the human body.

This diagram on the board comparing a biologic used to treat anemia and a traditional drug that treats peptic ulcers disease demonstrates the difference between traditional chemical drugs and biological therapies. As you can see, the biologic is significantly more complex than a traditional drug, have a molecular weight of 30,000 versus 351. This is a critical distinction between traditional generic drugs and follow-on biologics. Any regulatory pathway must take full account of this distinction, which for now seems to point to the inescapable conclusion that clinical trials on some level will be essential to ensure the safety and efficacy of follow-on biological products.

With the, again I want to thank you, Mr. Chairman, for spurring a discussion on this important subject. I look forward to hearing from our distinguished panel of witnesses.

[Prepared statement of Mr. Davis of Virginia follows:]

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Chairman WAXMAN. Thank you very much, Mr. Davis.

Without objection, all members will be permitted to enter an opening statement in the record. Do any members wish, however, to make any comments before we hear from our 15 witnesses? Mr. Issa?

Mr. ISSA. Thank you, Mr. Chairman. I will be brief. I will put my formal statement in the record, particularly because it sounds an awful lot like Mr. Davis'. The view is somewhat the same, and that is that it is very clear that we know a great deal about chemical compounds and we can say a chemical is a chemical, but, for example, Mr. Chairman, would you want to have these two oranges substituted as though there were no difference? Would you accept that a Florida orange is the same as a California orange if you have to peel it, Mr. Chairman? And, for Mr. Sali who is not here today, do you really think that any Russett potato is an Idaho potato and should be interchanged and have no value, no second testing of whether or not it makes a good french forestry?

Now, clearly we know how to make grain alcohol, and if I am buying grain alcohol, Mr. Chairman, it is very clear that I know that it is alcohol plus about 3 percent water that just gets in if you get the air to it. But, Mr. Chairman, do you really think that a $90 bottle of California wine that says merlot is equal to this fine boxed merlot? And would

you want to go to the dinner table or the hospital and have them interchanged without your prior approval, or perhaps a little taste?

This is biologics. These are made by process. Mr. Chairman, they may both be a merlot, but as a Californian, I am sure that you would not want them interchanged without your prior approval.

With that, I yield back.

[Prepared statement of Mr. Issa follows:]

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Chairman WAXMAN. Mr. Davis?

Mr. DAVIS OF ILLINOIS. Yes, Mr. Chairman, I would like to make a brief statement.

Chairman WAXMAN. Before I recognize you for that purpose, I would like to inquire if you have any props.

[Laughter.]

Chairman WAXMAN. The gentleman is recognized.

Mr. DAVIS OF ILLINOIS. Thank you very much, Mr. Chairman. I shall, indeed, be brief. But first of all let me thank you for calling this hearing.

In 1984 the landmark Hatch-Waxman Act provided a cost-effective alternative to branded drugs with the creation of a traditional generic pharmaceutical industry. Today's hearing marks yet another landmark as we are being called upon to address escalating biopharmaceutical costs.

This issue is near and dear to me, one, as a former health administrator, but also because my Congressional District has more hospitals and more hospital beds than any other Congressional District in the Country. Illinois has about 200 hospitals, most of them nonprofit. State hospitals are losing money, and another third are barely breaking even, notwithstanding cuts in Medicare and Medicaid.

According to Crane's Chicago Business, on February 13, 2006, while the State of Illinois has implemented prescription drug assistance programs like the Senior Care

Pharmaceutical Program, State Pharmaceutical Assistance Plan, All Kids Program that provides health insurance coverage and prescription drugs to children across all socio-economic groups, they help to buffer costs.

However, the sad reality is that cuts in Federal spending tend to shift costs to insured patients and their employers. By definition, health care is eating up a piece of our income, which is especially bad news for the 26 percent of Chicagoans, including 164,203 with full-time jobs and 43,876 with at least a college education who lack health insurance. These data are particularly disturbing when you take into consideration the median household income for Chicago is $38,625 a year.

With this in mind, I welcome today's distinguished panelists and look forward to their insight and recommendations on how we can build upon the foundation of generic competition for our consumers laid some 23 years ago under the Hatch-Waxman Act towards the attainment of a pathway to safe and affordable biotech drugs.

I guess if I was to have any kind of prop, I'd just take this water, which is pretty pure, and be delighted to have it.

Again, thank you, Mr. Chairman, for having this hearing.

[Prepared statement of Mr. Davis of Illinois follows:]

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Chairman WAXMAN. Thank you very much, Mr. Davis.

Does any other Member wish to be recognized for an opening statement? Mr. Yarmuth?

Mr. YARMUTH. Mr. Chairman, two things real briefly. First of all, I hope that Mr. Issa would accept an amendment to his list in saying that no self-respecting Kentuckian would accept Tennessee sour mash whiskey for a Kentucky bourbon.

Mr. ISSA. Now that is bipartisan if I ever saw it.

Mr. YARMUTH. Thank you.

Also, I would like to say that I think the Chairman and Mr. Davis have very accurately expressed and illuminated the conflicting issues that we have to deal with on this topic.

I would also mention the fact that we have to recognize that much of the research that leads to the development of these drugs and these medications, both pharmaceutical and also these biologics, are funded by taxpayer dollars initially, so that we have an overriding mandate to do what is best for the taxpayer, who is paying for most of this research at the very foundational levels.

Thank you, Mr. Chairman.

[Prepared statement of Mr. Yarmuth follows:]

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Chairman WAXMAN. Thank you very much.

We will now hear from our witnesses today. Our first witness I am pleased to welcome is Dr. Janet Woodcock. She is the Deputy Commissioner for Operations and Chief Medical Officer of the Food and Drug Administration.

Since you are standing, I will have you continue to stand because it is the practice of this Committee to put all witnesses under oath.

[Witness sworn.]

Chairman WAXMAN. The record will indicate that you answered in the affirmative.

We are delighted to have you here. We will put your full statement in the record. If it is possible, we would like to ask you to keep to around five minutes.

STATEMENT OF JANET WOODCOCK, M.D., DEPUTY COMMISSIONER FOR OPERATIONS AND CHIEF MEDICAL OFFICER, FOOD AND DRUG ADMINISTRATION

STATEMENT OF JANET WOODCOCK

Dr. WOODCOCK. Thank you. Mr. Chairman and members of the Committee, I am Janet Woodcock, Deputy Commissioner and Chief Medical Officer of the Food and Drug Administration. I thank you for the opportunity to testify about the scientific and regulatory framework surrounding follow-on biologics.

In considering the complex scientific issues at hand, I have relied not only on my experience leading the Center for Drug Evaluation and Research for over a decade, but also on my eight years of experience working in the Center for Biologics Evaluation and Research, or CBER. While in CBER I served as Acting Deputy Center Director and as Director of the Office of Therapeutics, in which capacity I oversaw the approval of biotechnology products to treat serious illnesses such as cancer, multiple sclerosis, and cystic fibrosis.

The success of FDA's generic drugs program has spurred interest in considering abbreviated application pathways for more-complex molecules. Currently there are over 9,000 approved therapeutically equivalent generic drugs on the

market. They constitute about 60 percent of prescriptions written in the United States. FDA's Office of Generic Drugs currently approves generics at the rate of more than one per calendar day.

The success of the program has stimulated competition. for the last decade, the rate of submission to the Office of Generic Drugs has rapidly increased. Submissions doubled between 2002 and 2006, to a current rate of about 793 applications per year.

The office has implemented numerous process improvements, have improved increased efficiency of the review process, and recently, as part of FDA's initiative on pharmaceutical quality for the 21st century, OGD instituted the question-based review. Eventually it is hoped this change will decrease submission of manufacturing supplements by about 80 percent, and thus free up more time of the reviewers to deal with this increased submission rate.

While the generics program has been very successful for small molecules, scientific challenges remain. We do not have good bio-equivalents methods for inhaled or many topical medications, and must require clinical trials to demonstrate equivalence. This has inhibited consumer access to generic versions of these types of products.

In addition, a number of drugs are made from complex molecules. In these cases, it can be difficult to tell

whether a proposed generic version is structurally identical to the innovator product.

Recently, as part of its critical path initiative, FDA has been evaluating the science needed to address these issues for generic drugs and is planning to lay out the scientific research that is needed to improve the process, as we did a number of years ago for innovator medical products.

The topic for discussion today is variously referred to as follow-on proteins, follow-on biologics, generic biologics, as well as other labels. Many of these terms are very imprecise and confusing, and I hope we can discuss terminology.

Largely, these terms are intended to refer to biotechnology produced protein products. In the U.S., such products are regulated either as drugs under the Food, Drug, and Cosmetic Act, or as biologic products under the Public Health Service Act. Whether regulated as drugs or biologic products, proteins fit into the category of complex molecules that can be difficult to fully characterize.

Copies of protection products that are regulated as drugs may be considered for the abbreviated applications pathways that exist under section 505. The very simplest peptide products may be able to demonstrate that they contain the same active ingredient as the innovator product, and thus may be considered under 505(j), what is commonly regarded as

the generic drug pathway.

In contrast, copies of approved protein products that are drugs would currently be considered for abbreviated applications under 505(b)(2), and the reason for this is that scientific techniques are not available to demonstrate sameness of these types of molecules.

The degree to which any abbreviated pathway could be used for any given protein depends on many factors, including its physical complexity, the availability of functional assays to characterize it, and its clinical use.

An abbreviated pathway does not exist for copies of protein products approved under the PHS Act. FDA has approved several follow-on proteins under 505(b)(2), including a recombinant hyaluronidase and recombinant version of human growth hormone.

We are currently preparing a guidance document on the general scientific framework for preparation of abbreviated applications for follow-on proteins under 505(b)(2). We expect to follow this with guidance on technical issues such as immunogenicity, dealing with immunogenicity of proteins and physical characterization methods.

I will be pleased to answer your questions regarding these complex issues.

[Prepared statement of Dr. Woodcock follows:]

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Chairman WAXMAN. Thank you very much, Dr. Woodcock.

As you mention in your testimony, for over ten years FDA has allowed brand name manufacturers of biotech drugs to make certain changes in the process by which they manufacture their products, but without repeating all the original clinical trials, under something called comparability protocols. I am interested in understanding the scientific rationale for allowing brand name manufacturers to make process changes without new clinical trials. I am also interested in its applicability to follow-on and biogeneric products.

What was the scientific basis for FDA's conclusion that clinical outcome trials are not necessary to assess the effects of certain biological product changes?

Dr. WOODCOCK. Manufacturing changes and process changes are undertaken for all pharmaceutical products, whether drugs or biologics. In each case we have to determine whether or not the change could result in any clinically significant change in the product, whether it is a small molecule or whether it is a large, complex molecule of some kind. FDA has a long history of quality regulation, putting into place procedures, both physical characterization of the new product and comparing it to the old product, functional characterization of a new product compared to the original product, and sometimes clinical characterization of a new

product. It depends on, as I said in my oral testimony, how much science we have available to assess these changes.

If we can be sure, based on a structural characterization, which we often can for a drug, then that would be sufficient for a small molecule drug. If that structural characterization isn't enough to assure that the new version is similar to the old version, then other types of tests might be necessary. And in some cases we might even require clinical tests.

For example, with small molecule drugs, when the formulation is changed we may require new bioequivalent studies.

Chairman WAXMAN. So that is completely within your discretion based on whether you think it is appropriate to have further evaluations, further studies?

Dr. WOODCOCK. Yes. There are multiple scientific issues that come into play in any given manufacturing change.

Chairman WAXMAN. I know most of these comparability decisions involving biotech drugs or any other drugs are confidential, but with the biotech drug Avonex the information is public. I assume you are familiar with that case?

Dr. WOODCOCK. Yes.

Chairman WAXMAN. What kinds of process changes did FDA permit in that case without repeating the original safety and

effectiveness trials?

Dr. WOODCOCK. In that case the original cell line that had been used to manufacture the product that was used in the clinical trials was no longer available, so the manufacturer had to go back and redo all of that and duplicate the manufacturing process that had been used for the original product. That is well described publicly. They made some original attempts. Those weren't successful.

They made some subsequent attempts and then extensive amount of comparison was made between the original product and the second version of the product, both the kinds I just described, both physical/chemical comparisons, functional comparisons, and so forth, so that at the end of the day it was decided that the products were similar enough that FDA could extrapolate from the clinical data that was derived for the first product to the new product.

Chairman WAXMAN. Were the changes between the two products significant?

Dr. WOODCOCK. The products were very similar, ended up being very similar.

Chairman WAXMAN. I meant the process changes. Were they significant?

Dr. WOODCOCK. The manufacturer attempted to duplicate the similar process that was originally done with the first product, but it was in a different site, in a different

scale, and so forth, so there were differences. It was not the identical cell line. It wasn't the identical product that had been made, and so forth.

Chairman WAXMAN. Are these changes similar to the kinds of changes that might be required to manufacture a follow-on product?

Dr. WOODCOCK. The difference between that example and the instance where a new manufacturer would attempt to manufacture a follow-on product would be that in the Avonex case the manufacturer had access to all the information about the process of manufacturing the first product. That is very important information, because it has information on all the intermediate steps and what happens during the manufacturing and purification process, and so on.

Chairman WAXMAN. Thank you.

Mr. Davis?

Mr. DAVIS OF VIRGINIA. We will start with Mr. Issa.

Chairman WAXMAN. Mr. Issa?

Mr. ISSA. Thank you. Thank you, Mr. Chairman, and thank you, Ranking Member Davis.

Avonex appears to be an example sort of--I will use a different wine than the one here, but you are talking at the Rothschilds trying to duplicate after they have had to clear their grapes away and put a new crop in. You have got the same maker with the same wine masters--in this case

scientists--trying to duplicate what they had already made. is that roughly correct? You may not be a California wine drinker, so I know it can be challenging.

Dr. WOODCOCK. I love California wine.

Mr. ISSA. You won't love the one here in this box. Trust me.

Dr. WOODCOCK. Yes. As an analogy, that is quite reasonable.

Mr. ISSA. Okay. So the next step that the Chairman's legislation or the legislation we are hearing here today would attempt to do is to say that, even though you had to sort of teach or go through a process, a re-learning process, even with the original designer, you are going to try and transfer this to a different winery, and they are going to try to get up, but they are not going to have the right to every trade secret, if you will. Not every nuance of the process is, in fact, in the public domain; is that correct?

Dr. WOODCOCK. That is correct. We face that now with our generic drug program.

Mr. ISSA. Okay. And you mentioned earlier that you have had chemical equivalents that didn't work out so well when they went generic, so to speak, even among name manufacturers. When an insurance company does a formulary and says this is equal to this, that is not always right, is it? There are side effects that are unanticipated often?

Dr. WOODCOCK. The generic drugs that we approve are fully interchangeable with the innovator drugs. They are therapeutically equivalent.

Mr. ISSA. You have never had a side effect?

Dr. WOODCOCK. We have numerous reports of side effects; however, we investigate those and we have extraordinarily rarely found any instance where there would be therapeutic inequivalence between a generic drug and an innovator drug.

Mr. ISSA. Now, when we get to biological and follow-on immune problems that occur, that is a different problem that you are not presently seeing as much in small cells but you do see it in biologics, don't you?

Dr. WOODCOCK. Yes. Proteins are what is called immunogenic. They produce often an immune response in people when they are administered.

Mr. ISSA. So if two otherwise the same follow-ons, the original and the follow-on, one could very much have a different immune response that would lead somebody who had successfully fought a disease to somehow develop a resistance; is that correct?

Dr. WOODCOCK. The immune response to a protein can cause many things. It can cause what you just said, which is neutralizing the effect, the beneficial effect of the protein.

Mr. ISSA. And then you could find yourself unable to

deal with either drug. In other words, you could make that change and find yourself opted out of the cure or the treatment?

Dr. WOODCOCK. That is true, and there are difficulties, for example, with insulin sometimes.

Mr. ISSA. So, given that you have this history, wouldn't, in the case of follow-on biologics, at least until this problem can be quantified, wouldn't you have a bias, an almost exclusive bias toward clinical trials, even if we gave you the jurisdiction and the right to shortcut those, limit those, eliminate them? From a standpoint of unsettled science, wouldn't it be proper to have clinical trials to ensure that that is not happening when, in fact, it can take someone who is surviving and put them in a position where they can no longer survive?

Dr. WOODCOCK. Currently--and, of course, I can only address the proteins that we are looking at under the 505, under the FD&C Act.

Mr. ISSA. Right, and you admit those are, by definition, less likely to be unknowns than the ones we are going toward; is that right?

Dr. WOODCOCK. No. That is where the terminology I think is very confusing. We have approved proteins under the Food, Drug and Cosmetic Act provisions under 505(b)(2), and in those cases, for those recombinant proteins we have looked at

the immunogenicity in people.

Mr. ISSA. Okay, but you have looked at them?

Dr. WOODCOCK. Yes.

Mr. ISSA. So, again, my one final exit question here in this short time: clinical trials are the only way to know whether substantially similar, substantially identical follow-on bio are, in fact, going to have differences in the immune response, or whatever term is appropriate; is that right?

Dr. WOODCOCK. Yes. We have very limited understanding of the basis of an immune response, and we are not able to fully predict immunogenicity in humans right now from non-clinical data.

Mr. ISSA. And this could be dangerous?

Dr. WOODCOCK. The immunogenicity must be evaluated.

Mr. ISSA. Thank you, Mr. Chairman.

Chairman WAXMAN. Thank you, Mr. Issa.

Mr. Yarmuth?

Mr. YARMUTH. Thank you, Mr. Chairman.

Dr. Woodcock, some in the brand name industry argue that any process for approving copies of biologics should follow the European Union model. The EU's governing directive, which is comparable to a statute, is extremely flexible and gives regulators great discretion to set procedures and standards and so forth.

The drug regulatory body there, the EMEA, has also established very particular procedures and approval standards to implement those directives. You are nodding, so you are obviously familiar with that process or that model?

Dr. WOODCOCK. Yes.

Mr. YARMUTH. And the biotech industry seems to like that public process that is used there for establishing and setting guidelines that contain the data requirements for biosimilars because the public gathering process allows those companies to help dictate what data their competitors must produce, and, of course, that would take a lengthy period of time.

Is the FDA required to undertake a public process for establishing data requirements?

Dr. WOODCOCK. No. We are not required to.

Mr. YARMUTH. Do you think it is scientifically necessary for FDA to engage in public guideline process to establish the data requirements for a follow-on protein product, scientifically necessary?

Dr. WOODCOCK. What FDA does currently is engage with the manufacturer in discussions--of course, those are not public--to provide advice on any manufacturer interested in pursuing a follow-on under 505(b)(2) process. But we often write scientific guidance for manufacturers because it provides better predictability and it provides, as you said,

transparency.

We are in the process of writing overall guidance on the process of scientific approach to follow-on proteins under 505(b)(2).

Mr. YARMUTH. Do you think that this process that the European Union uses, if we adopted that system here, would have the effect of freezing science at all? Is that a risk in doing that?

Dr. WOODCOCK. I am really not able to comment on that.

Mr. YARMUTH. Thank you, Mr. Chairman. I yield back.

Chairman WAXMAN. The gentleman has a couple minutes, would you yield your time to me?

Mr. YARMUTH. I would be happy to yield my time to the distinguished chairman.

Chairman WAXMAN. Thank you.

I just wanted to point out that the questioning by my colleague, Mr. Issa, about how you might need to have clinical trials to understand possible concerns, that is legitimate. FDA does now at the present time allow some changes in process without requiring clinical trials, but I do want to point out that the legislation that I have introduced would allow FDA to decide, when they think clinical trials are appropriate, to require clinical trials.

I do want to ask you this. In the use of comparability protocols limited to simple proteins, or can the manufactures

of more complex proteins make changes in their products without repeating the original clinical trials?

Dr. WOODCOCK. Yes, they can, if the science is there. It is very desirable for manufacturers of pharmaceuticals of any kind to make continuous improvements in their manufacturing process to maintain the quality of the pharmaceuticals as soon as possible and the efficiency of the process as good as scientifically possible. So FDA has adopted procedures, as I said, that allow manufacturers to make changes to their manufacturing process or perhaps open up new plants, say, if there is a demand for the product, and the amount of data that has to be generated really depends on the complexity of the product, how well we can physically characterize the product, how confident we are that that physical characterization will extrapolate to the same performance, but we may require many additional steps, up to and including clinical studies now, particularly of immunogenicity.

Chairman WAXMAN. Well, do you and other FDA scientists feel confident that comparability assessments provide adequate protection to patients from unsafe or ineffective biotech drugs?

Dr. WOODCOCK. The comparability assessment puts the burden on the manufacturer. The manufacturer must show to FDA's satisfaction that the change has not introduced anything that would be detrimental to the clinical

performance of the drug. So how much evidence is needed after a manufacturing change depends on how well the manufacturer can demonstrate that that product is going to perform the exact same way as the original product did in the clinical testing.

Chairman WAXMAN. And as science evolves, you will know better whether the comparability requires clinical tests or not; is that correct?

Dr. WOODCOCK. The ability to physically characterize protein molecules and other complex substances has evolved and is continuing to evolve, and so over time we are going to be able to do a better and better job of controlling the quality of these products and allowing for continuous improvement.

Chairman WAXMAN. Thank you very much.

Mr. Davis?

Mr. DAVIS OF VIRGINIA. I finally have my comparison up there. We talked before about how complex these are. This diagram up there, as you see, compares a biologic used to treat anemia and a traditional drug that treats peptic ulcer. It demonstrates the difference between the traditional chemical drugs and biological therapies.

Dr. WOODCOCK. Yes.

Mr. DAVIS OF VIRGINIA. As you can note on this, the biologic is significantly more complex than a traditional

drug.

Dr. Woodcock, you highlight in your testimony the importance of ensuring that facilitating the development of follow-on products through abbreviated pathways doesn't discourage innovation and the development of new biological products, and you refer to Hatch-Waxman as a balanced approach. Do you think an extended period of data exclusivity as well as certain patent protections like Hatch-Waxman has would help encourage innovation and development with biological products?

Dr. WOODCOCK. Sir, I am a doctor and a scientist, and that is really outside of my area of expertise.

Mr. DAVIS OF VIRGINIA. Okay, so you don't want to make the economic or policy determinations on that?

Dr. WOODCOCK. No.

Mr. DAVIS OF VIRGINIA. Okay. You also state in your testimony that demonstrating the similarity of a follow-on protein product to a reference product is more complex and would require new data. Does this mean FDA would require clinical safety data for follow-on biologics?

Dr. WOODCOCK. There is a very large range of complexity. All right? The erythropoietin molecule that you have here is a pretty complex example. There are very, very small biologic drugs of different kinds. So the amount of assurance and the amount of data that would be needed is

really based on how complex something is and how well it can be characterized in different ways.

Mr. DAVIS OF VIRGINIA. But a slight alteration could have, you know, significant clinical manifestations, wouldn't it?

Dr. WOODCOCK. FDA would not approve a follow-on product or a generic drug that we were not confident would have the same performance as the innovator drug.

Mr. DAVIS OF VIRGINIA. What level of clinical safety data would be necessary for approval, ball park?

Dr. WOODCOCK. Well, to talk about this we have to get into terminology a little bit. Please bear with me.

The abbreviated application process for 505(b)(2), for example, may rely on some fact of the approval of a prior product. All right?

Mr. DAVIS OF VIRGINIA. Yes.

Dr. WOODCOCK. But we may approve a product using an abbreviated application where some of the data, maybe some of the clinical trials or animal studies do not have to be repeated. However, that resulting of proof product is not considered substitutable for the other product. In other words, each of them stand alone and they can't be switched at the pharmacy, or it is not recommended they would be. That is one level.

Another level would be for a manufacturer to seek

interchangeability, full interchangeability. So far the proteins that we have approved all stand on their own. They have had abbreviated applications but they are not considered interchangeable with any of the other proteins in that class. For example, human growth hormone or hyaluronidase.

Mr. DAVIS OF VIRGINIA. You testified that the science and technology isn't sufficiently advanced to allow for comparison of complex protein products. How close are we to discovering those technology methods? Five years? Ten years?

Dr. WOODCOCK. It is going to be a continuum, and right now we are very short peptides, which are as small as the ranidine molecule you are showing there, for example, or in the same ball park. We can do it now, but those are very, very small compared to the erythropoietin molecule, so it is going to be a step-wise progression over a decade or so.

Mr. DAVIS OF VIRGINIA. Are there any non-clinical tests or technology that could fully substitute for studying the safety of biotech products in humans?

Dr. WOODCOCK. As I said, right now we do not have the science around the immune system to adequately predict the human immune response fully to any given product.

Mr. DAVIS OF VIRGINIA. You listed two examples, omnitrope and--I can't pronounce the other one. Hyaluronidase?

Dr. WOODCOCK. That is pretty good.

Mr. DAVIS OF VIRGINIA. Neither was rated by FDA as therapeutically equivalent or substitutes for other biologics on the market. Many believe interchangeability or substitution is where the most cost savings would occur. Of course, the balance here is safety versus efficiency and speed to market.

When do you think the FDA will be able to rate a biologic product as interchangeable? And do you think the FDA needs this authority if the science isn't developed yet?

Dr. WOODCOCK. For the 505(b)(2) drugs, which is what I can comment on, manufacturers would need to do additional clinical studies that would demonstrate interchangeability, and that is a further step. That is a higher bar than simply getting on the market, an abbreviated application. Does that make sense to you?

Chairman WAXMAN. Thank you, Mr. Davis.

Mr. Welch?

Mr. WELCH. Thank you, Mr. Chairman.

Some of the drug companies have said that when a biotech product is derived from a specific cell line, any copy of the product will have to begin with a different cell line. They are arguing, as I understand it, that this change is so significant that all the clinical trials, all the clinical trials must be repeated to ensure that the change has not

altered safety and effectiveness. Obviously, we are concerned about safety, but we also want to get the benefit and not have this argument about safety be used to deny us the benefit.

My question to you is: is it true that a change in a cell line will always necessitate repeating the original clinical trials?

Dr. WOODCOCK. No. We do not believe that. Again, any manufacturing change, whether the cell line, the DNA construct, the manufacturing process, the way the drug is purified, any of these could affect safety and effectiveness, and therefore data has to be submitted and a very careful look has to be taken to make sure that it hasn't. The amount of data that we would need or that anyone would need to make that evaluation depends, again, on the complexity of the product.

Mr. WELCH. All right. So the bottom line here is that you believe that you do not need, for safety, to repeat the entire clinical trial?

Dr. WOODCOCK. In some instances the manufacturer may not be able to show enough similarity and they may have to repeat much of the clinical program. In other instances they may be able to show an extreme amount of similarity, a very great similarity to prior product, and therefore would have very much smaller clinical trials needed, perhaps of

immunogenicity.

Mr. WELCH. And that is an evaluation that you would feel confident, based on the information that you had at hand, that you could make?

Dr. WOODCOCK. Yes. FDA has a long history, as I said, of controlling the access to market after manufacturing changes for a very wide number of products for all pharmaceuticals on the market, and this is another example of that.

Mr. WELCH. I was going to ask another question, but you are starting to answer it. What scientific developments have allowed FDA to feel that confidence you are describing, that manufacturers of existing biologics can change cell lines, manufacturing facilities, and/or the fermentation processes without having it conduct those clinical trials?

Dr. WOODCOCK. Yes. And, as I said, sometimes they do and sometimes they don't. It really depends. The burden is on them, the manufacturer, to show through scientific data that the performance of the product after the change process is going to be the same as the performance of the product before the change.

Mr. WELCH. And are clinical trials always the most sensitive studies for detecting changes in safety or effectiveness due to process changes?

Dr. WOODCOCK. No. No, I think that is a common

misconception. Clinical trials may be insensitive to certain types of changes, adverse effects, for example, that are rare or uncommon.

Mr. WELCH. Yes.

Dr. WOODCOCK. And we really need to use the scientific tool to assess the change in the product that is appropriate. It might be physical characterization or it might be a functional test. It might be evaluation of the purity of the product.

Mr. WELCH. Thank you. I yield the balance of my time.

Chairman WAXMAN. Thank you for yielding. You have another minute left on your time, so if the gentleman would permit I will take that minute if he will yield to me.

Dr. Woodcock, if FDA were given broad authority to require any studies necessary for approval of follow-on versions of PHS Act approved protein products, are you comfortable that the Agency could use its discretion to ensure that only safe and effective products were made available to patients? I think you have answered that question several times, but let me just put it very clearly.

Dr. WOODCOCK. I think that FDA must do that. All right? We do not currently approve generic products unless they have absolutely met our standards and were follow-on products under 505(b)(2). We must maintain the confidence in our program and also our own scientific integrity.

Chairman WAXMAN. Based on your experience with the comparability guidance, can you give the Committee a perspective on how often companies must do clinical outcome trials, not just PK or PD studies, to support a product or process change after approval of its BLA? Are large clinical outcome studies scientifically essential to support the approval one out of ten post-approval product changes, one out of twenty post-approval changes, or one out of fifty changes?

Dr. WOODCOCK. I would say that the factor that is most important here is the magnitude of the change; however, it is probably more in the one in fifty range than the one in ten, or whatever. But don't forget there are many different types of changes that occur all the time to manufacturing processes. If you included all of those, then requiring clinical studies of outcomes would probably be quite rare.

Chairman WAXMAN. Thank you.

Mr. Bilbray?

Mr. BILBRAY. Mr. Chairman, I would like to yield my time to the gentleman from the Northwest Territory, but I would first like to clarify that, as a native Californian as opposed to Mr. Issa who is an immigrant, I was outraged at the concept of bringing a bottle of merlot to this table and having it chilled.

[Laughter.]

Mr. BILBRAY. The only thing worse than that is to take it from the table and take it back to his office after he presented it.

But at this time I would like to yield to Mr. Burton.

Mr. BURTON. I thank the gentleman for yielding. I am from the midwest, not the northwest.

Mr. BILBRAY. Well, the Northwest Territory.

Mr. BURTON. Ohio, the Northwest Territory. You are going back a long way.

First of all, let me preface my remarks by saying the pharmaceutical industry and FDA working together has created probably the highest quality of life in the history of mankind, and I appreciate that and I think everybody in America does. There are some questions, though, that I have to ask about the process.

You said it is a judgment call on whether or not this product comes to market. Who makes the judgment? Who makes the call?

Dr. WOODCOCK. The FDA.

Mr. BURTON. Don't they have advisory committees that review the process, review the product, review the results, and then they make a recommendation to the FDA?

Dr. WOODCOCK. Yes. Advisory committees are frequently utilized, particularly on clinical decisions. Here we are talking about scientific characterization of the product in a

wide variety of ways. Most often, that is something that the FDA scientists do.

Mr. BURTON. But the FDA does have advisory committees for almost all of the products?

Dr. WOODCOCK. Yes.

Mr. BURTON. When I was chairman I asked--I don't believe it was you, but I asked one of your coworkers who was a leader at the FDA how many times has an advisory committee recommendation been turned down by the FDA.

Dr. WOODCOCK. You are asking me?

Mr. BURTON. Yes.

Dr. WOODCOCK. I don't know the answer to that.

Mr. BURTON. I will tell you what it was before. It was never. The advisory committee, I was told by the people who were doing the investigation for my Committee when I was chairman, was that the advisory committee recommendations were always accepted.

Now, the other thing I would like to know is: the people on the advisory committee, do they file financial disclosure reports?

Dr. WOODCOCK. Yes, they do.

Mr. BURTON. We looked at some of the financial disclosure reports when I was holding hearings on this when I was chairman and we found that many of the people in the advisory committees did not file financial disclosure

reports. And we found that some on the advisory committees had a conflict of interest. The RotoShield virus was one of those. The head of the advisory committee had an interest in a company that was going to make a RotoShield virus vaccine, which was put on the market at his advisory committee's recommendation, and FDA approved it based upon the recommendation. One or two children died and several people were injured and they pulled it off the market within 12 months.

I bring this up because this is a very important issue we are talking about today, and I would just like to ask that these advisory committees, when they make recommendation, that there is a thorough judgment made after the advisory committee makes its determination, and that the FDA does not always accept their results or their recommendations, and that there are complete financial disclosure reports.

The reason for that is pretty obvious. If a person is on an advisory committee and their recommendation is accepted and they have a financial interest in a pharmaceutical company that is going to manufacture a product like that or a like product, they are liable to have their judgment tainted just a little bit. It has happened in the past and I hope it doesn't happen in the future.

The cost of biotech drugs increased 17 percent from 2005 to 2006, and that was compared to 5.4 percent increase for

traditional pharmaceuticals, which are much more expensive here than in some other countries, in most cases. Why was that increase so much? Do you know?

Dr. WOODCOCK. My understanding is that some of the new biotech products on the market that are very highly effective, you know, are very expensive to purchase, as some of the Members already alluded to. But I don't have any complete analysis of this.

Mr. BURTON. I have a couple more questions, but I will wait.

Chairman WAXMAN. We will have another round.

Mr. BURTON. I will catch it next time.

Dr. WOODCOCK. May I?

Chairman WAXMAN. Yes.

Dr. WOODCOCK. The FDA has recently published new guidance on advisory committee conflict of interest, and it lays out very explicit and transparent guidance on how people will be evaluated for their conflicts of interest.

Mr. BURTON. That is very good news. I appreciate hearing that. That is a great step in the right direction. Thank you.

Chairman WAXMAN. Thank you, Mr. Burton.

Mr. Davis?

Mr. DAVIS OF ILLINOIS. Thank you very much, Mr. Chairman.

Dr. Woodcock, I have always tried to understand--and if you could enlighten me it would be very helpful to me--the real difference between generic drugs and the name brand. If they do essentially the same thing or if the level of effectiveness is essentially the same, why do we pay so much more for one as opposed to the other? I have never been able to, in my own mind, feel that I had a real understanding of that.

Dr. WOODCOCK. Well, if I may, if you look at the diagram--it is gone now, but there was a diagram of the molecule up there, a small molecule. We know exactly everything how that molecule is structured. We know everything about it. And so what we do in the generic drug program is we require an exact copy of that molecule to be the generic drug and then we make sure that that molecule gets into the body the exact same way that the innovator molecule gets into the body. So then we say if it does that it is going to have the same effect on the body because it is circulating around in the body the same way as the innovator drug. So that is what a generic drug is.

The problem with the proteins is it is very difficult to say we have the exact same molecule because it is such a complicated molecule.

Mr. DAVIS OF ILLINOIS. The effectiveness or the impact, are we saying that we would expect a different level of

impact or effectiveness using one as opposed to the other?

Dr. WOODCOCK. For the generic drugs that FDA approves we expect the exact same performance. Now, that means the exact same good effects and the exact same side effects as the drug it is a copy of.

Mr. DAVIS OF ILLINOIS. Do you know then how the price or cost differential emerges or is determined?

Dr. WOODCOCK. Well, while the innovator drug is patent protected or protected by exclusivity, there is no other copies available to be prescribed. During that time the price is quite high. Once generic versions get on the market, the price of the various generic copies becomes only a fraction of what was charged by the innovator.

Mr. DAVIS OF ILLINOIS. Are you aware or familiar with any consumer studies that would indicate whether or not consumers have a greater level of confidence, for example, in the more popular pharmaceuticals than the generics?

Dr. WOODCOCK. Certainly the generics are not advertised and certainly there is some brand name loyalty that I have heard of. I have certainly talked to many, many consumers over my lifetime about this issue. There is some residual concern still about the generics and are they as good because they are not the brand name product; however, I think in the last 10 or 12 years of our generic drug program, confidence, both by the health professionals--the pharmacists, the

doctors--as well as the consumers has really risen, and most people in this country are used to taking generic versions.

Mr. DAVIS OF ILLINOIS. And so then one could probably reasonably assume that marketing plays a great role in shaping our attitudes and thoughts about the drugs that we would most likely prefer using?

Dr. WOODCOCK. I can't comment on that directly, but that is one of the purposes of advertising.

Mr. DAVIS OF ILLINOIS. And so I would assume that it probably works fairly well and that it does, in fact, skew one's thinking. And if we are talking about having the most cost-effective health care, then it just seems to me that the more enlightened consumers become, that will probably have as much impact on cost effectiveness in health care as anything that we are going to regulate or anything that we are going to do.

I thank you very much for your answers.

Dr. WOODCOCK. At the request of Congress, we had an education program, outreach program, on the generic drug program. It has been very effective.

Mr. DAVIS OF ILLINOIS. Thank you. Thank you very much.

And thank you, Mr. Chairman. I yield back.

Chairman WAXMAN. Thank you, Mr. Davis.

Mr. Burton was using Mr. Bilbray's time, and he said he had a few more questions, so before we go to a second round I

yield to you your first-round five minutes.

Mr. BURTON. Thank you. I just have a few more questions.

Dr. Woodcock, I think you have been very helpful, some of your answers today. I really appreciate that.

The pharmaceutical industry deserves to get some of their money back or all of their money back when they spend a lot of money on research and development, and that is why the patents are there, and then when it expires, of course, it can be a generic drug and they should have recovered their investment.

Are other countries working to develop these biotech drugs?

Dr. WOODCOCK. Yes. As was alluded to earlier, the European Union has published a directive and is implementing a program on what they call biosimilars. By that generally they mean biotech drugs.

Mr. BURTON. If they produce a biotech drug and there is a similar biotech drug that has been produced here in the United States, because of the differences, the scientific differences that you were talking about when we saw the slide a while ago, the FDA probably would not allow that drug to be imported into the United States until it was approved by the FDA, even though it did the same thing or pretty much the same thing?

Dr. WOODCOCK. Yes. The law doesn't allow drugs to be imported in the United States unless they are approved.

Mr. BURTON. Let me ask you this one more question. If we had reimportation or importation of the pharmaceuticals that are approved by the FDA, would the prices of those pharmaceuticals be lower?

Dr. WOODCOCK. Again, this is beyond my area of expertise. I apologize.

Mr. BURTON. I will just follow up by saying that everybody wants free enterprise to succeed and they want the pharmaceutical industry to make a lot of money so that they can do continued research, but when my first wife had cancer--and I have talked about this before--we went to have her chemotherapy and the tamoxifen that one woman was taking, she was complaining about the cost being about $300 a month, and another lady said I'm getting the same thing from Canada for $50 a month, so it was six times less.

There are a number of us in Congress that would like to see the FDA working with their counterparts in other countries and the pharmaceutical companies working with their counterparts in other countries and the governments of other countries to find out some way to level the playing field so that Americans are paying a comparable price for their pharmaceutical products as they do in other countries. It just doesn't seem fair to go to Germany or France or Spain or

Canada and find that the very same product is being sold for much less and Americans are paying actually a great deal more for the research and development and the advertising than is being done elsewhere.

That is just a suggestion. I appreciate very much your candid answers.

I yield to the chairman.

Chairman WAXMAN. Thank you very much for yielding. The gentleman has a minute and a half, so I will be glad to take it.

If a statute were passed giving FDA broad authority to review abbreviated applications for follow-on proteins, and if companies were ready to begin submitting applications as soon as the statute became law, is it reasonable to assume that FDA would be able to begin reviewing those applications as soon as they were submitted, assuming, for purpose of this question, that the statute did not require FDA to issue regulations or guidance as a prerequisite to review of applications?

Dr. WOODCOCK. FDA is currently, as I said, reviewing applications and also inquiries from companies and so forth, providing guidance for drugs under the 505(b)(2) regimen. So we have the technical expertise to perform these functions.

Chairman WAXMAN. Thank you.

Mr. Hodes?

Mr. HODES. Thank you, Mr. Chairman.

Dr. Woodcock, I want to focus for a moment on the issue of comparability.

Dr. WOODCOCK. Yes.

Mr. HODES. It is my understanding that biologics as a group are so diverse and in some cases so incompletely understood that there is today no one-size-fits-all set of studies that can demonstrate comparability. Is that true?

Dr. WOODCOCK. Absolutely. Biologics, as opposed to biotech proteins, biologics range from everything from gene therapy to cells, living cells of different types, to tissues--a huge range of different kind of products.

Mr. HODES. And am I correct that biopharmaceutical products often undergo changes after approval and that pre-change and post-change products will be comparable, as opposed to identical?

Dr. WOODCOCK. Yes. As we were discussing before, manufacturers need to continue to improve their process or they may need to open up new plants or increase the level of production, the scale of production. There are a lot of changes that have to be made. After each one of those changes, we must assess whether or not the performance of the product has changed.

Mr. HODES. And the FDA establishes boundaries and batches. Different batches have to fall within established

boundaries for that product?

Dr. WOODCOCK. Yes. Any product, whether it is a small molecule or drug, has slight variations lot to lot in any kind of testing parameter that you would put on it, so the traditional approach is you establish boundaries within which a product can vary, but it can't go outside of those limits.

Mr. HODES. Now, just as the science is evolving on the manufacturing side, certainly from the FDA's standpoint techniques for assessing the structure and activity of biologics are evolving rapidly, and our understanding of biological structure and activity is improving all the time; is that correct?

Dr. WOODCOCK. That is correct.

Mr. HODES. If Congress were to tell the FDA what specific types of clinical data must always be required for approval of follow-on biologics based on today's science, could such clinical data requirements become obsolete?

Dr. WOODCOCK. Certainly, from my point of view, flexibility in enabling us to incorporate the new science into the regulatory process as that science evolves and becomes available is in the best interest of the public as well as the Agency and the industry.

Mr. HODES. And if a follow-on statute required a clinical trial in every case, could it end up requiring perhaps unnecessary and therefore potentially unethical

trials in the future?

Dr. WOODCOCK. Where trials aren't needed it is, you know, of questionable ethics to repeat them. So use of human subjects for trials that are not needed or simply to check a box on a regulatory requirement are not desirable.

Mr. HODES. Let me ask you a question about the EU system. The EU regulations, as I understand them--imperfectly, I might add--require post-market surveillance; is that correct?

Dr. WOODCOCK. I can't speak exactly. The Europeans have the ability to require post-marketing surveillance for any approved pharmaceutical.

Mr. HODES. Does the FDA currently have any requirements for post-market surveillance?

Dr. WOODCOCK. We very frequently request post-marketing studies be performed at the time of approval, and those are agreed to by the firms.

Mr. HODES. So it is the manufacturers who are conducting the post-market surveillance?

Dr. WOODCOCK. Yes.

Mr. HODES. But from the FDA, the FDA relies on the manufacturers for that post-market surveillance; the FDA doesn't do any of its own?

Dr. WOODCOCK. Right. The FDA conducts the adverse event reporting system, which is an adverse event reports from

doctors and companies, and we do some limited studies, but in general we do not have the capacity to do post-marketing surveillance as you are describing.

Mr. HODES. Do you believe that with biogenerics developing as rapidly as the field is developing, that there should be expanded requirements for post-market surveillance?

Dr. WOODCOCK. All pharmaceuticals when they are approved for the first time have a fair amount of uncertainty still surrounding them about their performance, and particularly, as we have discussed already, any protein product that would be approved would continue to have questions about immunogenicity and perhaps other side effects that would probably need to continue to be looked at in the post-marketing period.

Mr. HODES. Can the FDA require post-marketing studies?

Dr. WOODCOCK. What we do is say to the company, You need to agree to conduct this study, and if you do then that is part of the approval is that the company agrees to do that.

Mr. HODES. So, if I understand your answer, the answer is yes, the FDA does have the authority to require post-market studies?

Dr. WOODCOCK. At the time of approval.

Mr. HODES. And what proportion of those post-market studies of those that you require are completed?

Dr. WOODCOCK. That is a complicated question. There are

many different types of studies that are requested, and some of them go on a long time, so there isn't a really high proportion. I don't know the exact number, because it depends on what analysis you are doing, but many of these studies are not completed.

Mr. HODES. And if you were the last word on this, thinking about where the science is going with biogenerics, do you see a need for increased requirements for post-market studies of these biogenerics, none of which will ever be identical, either in batch or in actual structure, to the original?

Dr. WOODCOCK. I believe it would be likely in many cases, but, as I said, this is going to be a case-by-case because of all the differences in the different products. In many cases FDA would need to have post-marketing surveillance or post-marketing studies done to resolve remaining uncertainties.

Mr. HODES. And, last question, does the FDA have an enforcement mechanism to require completion of any post-marketing studies that you have required of the manufacturers?

Dr. WOODCOCK. Our mechanism, we can publicize the fact that the studies have not been done, and we could take the drug off the market.

Mr. HODES. So the enforcement mechanism is the possible

removal of the drug from the market for lack of completion?

Dr. WOODCOCK. Yes.

Mr. HODES. Has that ever been done?

Dr. WOODCOCK. Not to my knowledge.

Mr. HODES. Thank you.

I yield back. Thank you, Mr. Chairman.

Chairman WAXMAN. Thank you. That is called the guillotine, except it is never used.

Dr. Woodcock, I understand that it is quite a bit more complicated to establish interchangeability of two protein products than to establish their comparable safety and effectiveness. Would it be possible to demonstrate that a copy of a well-understood protein is interchangeable with the brand name drug if there are no limits on what studies can be required?

Dr. WOODCOCK. We believe so. The situation in health care right now is that products that are interchangeable, they may be repeatedly switched back and forth. All right? And where you have a situation where you have a number of similar products on the market, the same indication, and they are very similar, it might be that they can be switched back and forth among one another multiple times for a given patient, depending on the plan and who they contract with and so on. In that situation either the innovator product could cause antibodies to the follow-on product or vice versa. We

think we would have to test that in people to make sure, but we think it would be feasible to do those tests.

Chairman WAXMAN. Is our understanding of protein structure and activity likely to evolve in a way that will make it possible to establish interchangeability in the foreseeable future, at least for some of these proteins, that may not be obvious at the present time?

Dr. WOODCOCK. It may not be the protein, itself, that causes the immune response, but it could be different contaminants that are co-purified from the cell line or during the manufacturing process, or it can be changes that happen late in manufacturing or during storage or so forth, so it is really a very complicated situation.

Chairman WAXMAN. For very simple, well-understood proteins, what kinds of studies might be required to establish interchangeability?

Dr. WOODCOCK. Well, a study that actually performs that activity, which changes the patient back and forth from one version of the product to the next and follows the immune response.

Chairman WAXMAN. Would that be a difficult study?

Dr. WOODCOCK. No. In some cases there might be ethical issues that we would have to address very carefully. We would not want to set any patient up for harm.

Chairman WAXMAN. Might the study requirements lessen

over time as the molecules are better understood?

Dr. WOODCOCK. Yes.

Chairman WAXMAN. Do you think that the FDA would ever declare a copy of a biotech drug regulated under Hatch-Waxman to be interchangeable if the Agency had doubts about whether it could be safely substituted for the brand name product?

Dr. WOODCOCK. No. I mean, we believe that our finding of an A rating of interchangeability is our word. We are saying that scientifically we believe those products would be interchangeable, and we would not do that unless we believed that were the case and it was substantiated with scientific data.

Chairman WAXMAN. Do you think that the FDA could be trusted to make appropriate interchangeability determinations for protein products if the Agency were given statutory authority to approve copies of biologics under the PHS Act?

Dr. WOODCOCK. I believe that the FDA can be trusted to carry out its mandate from Congress, whatever that might be.

Chairman WAXMAN. And if we gave you an additional mandate, you feel you would be able to live up to it?

Dr. WOODCOCK. Yes. I believe we have scientific expertise. As we have already discussed, we have been managing manufacturing changes for all pharmaceuticals on the market for a very long time.

Chairman WAXMAN. Thank you.

Let me see if any Member wishes additional time for questions?

[No response.]

Chairman WAXMAN. If not, let me thank you very much for your presentation and your willingness to answer these questions. I think it has been very helpful for us in our understanding of this issue. Thank you very much.

Dr. WOODCOCK. Thank you.

Chairman WAXMAN. The Chair would like to now call forward our second panel.

Dr. Geoffrey Allan is the President, CEO, and Chairman of the Board of Insmed Incorporated located in Richmond, Virginia. Insmed is a biopharmaceutical company focused on the development and commercialization of drugs for the treatment of metabolic diseases and endocrine disorders with unmet medical needs.

Dr. Theresa L. Gerrard is now the President of TLG Consulting, Inc., where she assists pharmaceutical and biotechnology companies in product development and regulatory strategy. Prior to that she spent 11 years as a Division Director in FDA's Center for Biologics Evaluation and Research, and she has also previously served as Director of Development for Amgen.

Dr. Bill Schwieterman is a physician and scientist by training who now acts as an industry consultant to major

biotech pharmaceutical companies on product clinical development issues. Dr. Schwieterman started his career at NIH and subsequently moved to FDA, where he worked for ten years and served as the Chief of Immunology and Infectious Disease Branch within FDA's Center for Biologics Evaluation and Research.

Inger Mollerup has been the Vice President for Regulatory Affairs at Nova Nordisk A/S since 2004. Nova Nordisk is a pharmaceutical company which focuses on diabetes care, as well as hemostasis management, growth hormone therapy, and hormone replacement therapy.

Dr. Ganesh Venkataraman is Co-Founder and Senior Vice President of Research at Momenta Pharmaceuticals. Momenta Pharmaceuticals, Inc., is a biotechnology company located in Cambridge, Massachusetts focused on the treatment of disease through an understanding of sugars and complex biomolecules.

We are pleased to welcome all of you to our hearing today. We appreciate your being here.

It is the custom of this Committee to put all witnesses under oath. You are not being singled out. I would like to ask you to please stand and raise your right hands.

[Witnesses sworn.]

Chairman WAXMAN. The record will reflect that each member answered in the affirmative.

We will make your prepared statements part of the record

in its entirety. We would like to ask, if you would, to try to limit the oral presentation to around five minutes.

Why don't we start with Dr. Allan, and then we will move right down the line. You see we do have a timer. Dr. Allen?

STATEMENTS OF GEOFFREY ALLEN, PH.D, PRESIDENT, CHIEF EXECUTIVE OFFICER, CHAIRMAN OF THE BOARD, INSMED INCORPORATED; THERESA LEE GERRARD, PH.D, PRESIDENT, TLG CONSULTING, INC. (BIOPHARMACEUTICAL CONSULTANTS) (FORMERLY WITH AMGEN AND FDA'S CENTER FOR BIOLOGICS); BILL SCHWIETERMAN, M.D., PRESIDENT, TEKGENICS CORPORATION (BIOPHARMACEUTICAL CONSULTANTS)(FORMERLY WITH FDA'S CENTER FOR BIOLOGICS); INGER MOLLERUP, VICE PRESIDENT FOR REGULATORY AFFAIRS, NOVA NORDISK A/S; AND GANESH VENKATARAMAN, PH.D, SENIOR VICE PRESIDENT, RESEARCH, MOMENTA PHARMACEUTICALS, INC.

STATEMENT OF GEOFFREY ALLAN

Mr. ALLAN. Good morning, Chairman Waxman, Ranking Member Davis, and members of the Oversight and Government Reform Committee. I am delighted to have the opportunity to testify before your Committee. The focus of my discussion will be the role of small, innovative biotechnology companies in the current debate regarding the development of a regulatory pathway for approving biogeneric drugs.

My name is Geoffrey Allan, and I currently serve as the Chief Executive Officer of Insmed, Incorporated. Insmed is a small biotechnology company focused on the development and

commercialization of drugs for the treatment of metabolic and endocrine disorders where there are clear unmet medical needs.

We received FDA approval for our lead product, IPLEX, at the end of 2005. IPLEX is a therapeutic protein which is approved for the treatment of children suffering from a rare growth disorder. We are currently continuing to develop IPLEX for several major medical illnesses such as myotonic muscular dystrophy and medical complications associated with HIV infection.

I am here today to talk about biogeneric drug development and the regulatory path forward. I believe our experience with IPLEX is very illustrative of the scientific and technical issues confronting biogeneric drug developers, issues such as comparability testing and the nature and extent of clinical trials needed to support characterization of a generic biologic. Our experience tells us that these issues can be addressed using sound, readily available scientific approach.

Insmed has developed significant intellectual capital focused towards protein characterization and purification. We have invested in building a facility required to manufacture quality proteins. The biogenerics business is a business in which we would like to specialize. The combination of our proprietary protein platform with a

biogeneric protein platform meets our goal to sustain innovation, along with the ability to provide safe and affordable drugs to address a growing economic issue.

It is my belief that there are a number of my colleagues in similar-sized companies that are also interested in providing the scientific expertise to meet the challenges of producing biogenerics. I believe that I am representing the interests of many smaller biotechnology companies and large contract manufacturing companies. I believe H.R. 1038 provides for a fair balance between reward and innovation in creating a timely approval pathway in commercialization of biogenerics in the marketplace; therefore, passing this bill would be a positive step for the biotech industry and continue to fuel the cycle of innovation.

As the Chief Executive Officer of a small biotechnology company, I hope my testimony will provide a different perspective on this important issue and bring to light some of the important reasons why this bill is the correct model to create a robust, competitive, and innovation biopharmaceutical marketplace.

IPLEX is a recombinant protein product. In fact, it is a combination of two different recombinant protein molecules. It is a relatively large molecule, larger than insulin, growth hormone, the interferons and Epogen, and certainly no less complex in its structural characteristics. As a new

drug, along with the demonstration of safety and efficacy in the target population, structural characterization of the protein and the development of quality manufacturing process was our central focus during the development of the product.

During the course of the development of this product, we modified the manufacturing process several times. We changed cell lines. We changed purification procedures. We changed raw material sources. And on more than one occasion we changed the facilities where this product was manufactured. At all times, good analytical methodology was the bedrock of our comparability testing to ensure that we produced a consistent, highly-purified protein.

Analytical methodology to allow structural characterization of proteins has evolved enormously over the years. It is sophisticated and has exquisite sensitivity. For example, we use a battery of sensitive an analytical tests. More than ten of these tests are used, one of which is a technology called mass spectroscopy. This technique has such high resolution that on certain molecules we can detect changes as small as a single proton within the molecule. This is essentially not a crude science.

During the development of IPLEX we worked closely with the FDA. They clearly used their discretion to decide what tests we needed to support our scientific approach as we made changes to our manufacturing processes. Their

recommendations were rationale and certainly not onerous. On the occasion that we changed the site of manufacture of the drug, moving our process from a U.K. facility to our own facility in Colorado, we conducted a simple pharmacokinetic study in human volunteers to establish the equivalence of the products after the facility change. We established very quickly, within one month, that the amount of drug in the bloodstream was consistent, regardless of where the drug was manufactured.

IPLEX was being developed for use in children, and as such both we and the FDA knew that safety at all times was paramount and was certainly never jeopardized. For example, FDA was concerned that immunogenicity of the product could vary as we changed the process. We established surveillance procedures to address this issue, and we continue to monitor for signs of immunogenicity today.

I have only given you a very brief overview of the type of scientific and technical issues we had to address in the development of this product, IPLEX; however, these issues are at the heart of what a biogeneric manufacturer would have to confront. The science has reached a level of sophistication to make this endeavor entirely possible. All we need now is the regulatory go-ahead.

The proposal introduced by Chairman Waxman is extremely appealing as a next step in stimulating competition in order

to address an ever-increasing economic problem facing our health care system. Based on our company's experience with the FDA during the approval process of IPLEX, I am confident that this legislation is based on sound science and progressive insight into where the market should be in the coming years.

Once again, thank you for this unique and important opportunity to share my experience and views. I look forward to your questions.

[Prepared statement of Mr. Allan follows:]

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Chairman WAXMAN. Thank you very much, Dr. Allan.

Dr. Gerrard?

STATEMENT OF THERESA GERRARD

Ms. GERRARD. Good morning, Chairman Waxman, Ranking Member Davis, and members of the Committee. My name is Theresa Gerrard. Thank you for allowing me the opportunity to testify this morning on the importance of establishing a science-based, abbreviated approval pathway for biogenerics.

From 1984 to 1995 I was with the FDA and was a Division Director with responsibility for IND and BLA review of hundreds of biotech products. I chaired licensing committees for Amgen's Neupogen, Genentech's Actimmune, and was involved in the review of beta Interferon from Chiron and Biogen.

After leaving FDA, I was Director of Development for Amgen in Boulder, Colorado, where I had oversight of development of several biotech products. For the past nine years I worked as a consultant, where I have worked with many companies, primarily brand biotech companies.

The purity of biotech products and the sophistication of analytical testing that exists today allowed the production of safe biotech drugs. Analytical testing consists of multiple sophisticated tests that are used to assess the

physical, chemical, and biological characteristics of the product. Many more tests are used to assess a biologic than are typically used to assess a drug, because biotech products are more complex than drugs.

These tests set the product specifications or goalposts, if you will, for every batch of biotech product that must fall between these goalposts. This is between no two batches of biotech products are identical. There are always minor variations.

The advances in analytical characterization for well-characterized biologics allowed FDA to develop scientific police officers on comparability in the early 1990s. This gave brand manufacturers the ability to change the manufacturing processes without the need for redoing the original clinical outcome trials if the product generated by the new process was shown to be comparable to product made by the old process.

Now, when we speak of biologic, the focus is on comparability. Why? Because no two batches of biologic product, whether brand or generic, will ever be identical. Therefore, biologics are and should always be discussed in the context of comparability. Yes, small changes in manufacturing could have an impact on the final product, but we have known this for more than a decade and can detect these changes.

For the past 15 years, FDA has gained substantial experience and expertise in assessing manufacturing changes and comparability data for a large number of protein products. The underlying scientific principles that guided comparability policy are still valid and can and should be adopted for generic biopharmaceuticals. Why? Because the types of post-approval brand product changes are reflective of the issues biotech and generic companies will face in bringing generic biotech products to the market.

The primary premise of comparability is that analytical testing is the most sensitive method to detect differences between two products. Clinical trials are rather insensitive in detecting product differences because the variation among people and their response to a biopharmaceutical does not allow one to detect subtle product differences. Analytical testing, by itself, will not be sufficient in every case to demonstrate that a generic will have the same safety and efficacy as the brand biotech product. In those cases, FDA can require additional data such as animal studies, human pharmacokinetic studies, or even clinical trials. There is not a one-size-fits-all model, but FDA can determine the amount of data needed based on the complexity of the product, the history of the clinical use, and the extent of analytical characterization to determine its comparability with the brand.

Before concluding, the question of immunogenicity has been raised in the discussion of both brand and generic biopharmaceuticals, and I would like to take a moment to just briefly touch on this topic.

Immunogenicity means the body generates antibodies to a specific foreign substance, such as bacteria, and it is a normal response in keeping people healthy. People routinely make antibodies to many different substances and experience no negative effects. Some biologics can cause people to generate antibodies which are specific to that product, but most will not have any affect on safety or efficacy. For some to imply that immunogenicity reactions are always harmful is just plain incorrect.

FDA can assess the risk for immunogenicity when it reviews the products for purity, safety, and overall quality and can request additional clinical data when necessary. While immunogenicity is an important consideration for biogenerics, it is certainly not a hurdle to their development.

Mr. Chairman, the science exists for a creation of a clear, efficient, abbreviated biogeneric approval pathway. Analytical tests, combined with additional data when needed, would ensure the safety and efficacy of generic biopharmaceuticals.

Thank you.

[Prepared statement of Ms. Gerrard follows:]

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Chairman WAXMAN. Thank you very much, Dr. Gerrard.

Dr. Schwieterman?

STATEMENT OF WILLIAM SCHWIETERMAN

Dr. SCHWIETERMAN. Good morning, Chairman Waxman and members of the Committee on Oversight and Government Reform.

My name is Dr. William Schwieterman. I thank you for the opportunity to appear before the Committee today and present the scientific and clinical perspective on the issue of biogenerics.

One of the most disturbing experiences for a physician is to know that a treatment is available to help your patient, but the cost may simply be beyond what your patient can afford. For this reason, I deeply share your goal, Congressman Waxman, of creating a sound, scientifically based approval pathway for biogenerics. And, given that I also had the privilege of working at FDA in the area of biotechnology for ten years, I know that your goal can and should be achieved.

I come before you today wearing three hats: as a physician, as a scientist, and as a former FDA reviewer. From this vantage point I would like to make the following critical points to the Committee:

First, with today's scientific advancements and technologies, we can assure the safety and efficacy of biogenerics.

Second, the supporting science for this is not new. It has existed for over a decade.

Third, the issues raised in post-approval brand changes are reflective of the issues that are raised in the field of biogenerics. As such, the same science that determines comparability for the brand tech industry can also be adopted to ensure the safety and efficacy of complaint and interchangeable biogenerics.

Having worked extensively with Agency physicians and scientists, it is clear to me that there is just one Agency safety standard, and that standard has been and will continue to be applied in the review and approval of each and every biologic, whether it be a brand or a generic.

The standards and science used for current biopharmaceuticals are informative to us with respect to biogenerics. A critical but not often publicized fact in the biopharmaceutical industry is that FDA does not require brand companies to perform large clinical outcome studies to retest the product generated by new manufacturing processes. This is because such an approach would not only be infeasible, but, more importantly, would ignore the utility of existing sophisticated scientific analytic tools and techniques for

this purpose.

Let me briefly summarize what happens in these instances. FDA starts with an assessment of extensive analytical comparability data. With these data, and keeping in mind the nature of the drug, the tests used, and the disease being studied, FDA decides how to proceed. The Agency can give a thumbs-up or a thumbs-down regarding each post-approval brand manufacture change and, if thumbs-up, have that change be supported by the analytic data, alone. The analytic data, coupled with pharmacokinetic and/or pharmacodynamic studies or the analytic data--the studies just mentioned--plus data from a large clinical outcome study.

As you already have heard, the vast majority of brand manufacturing changes need no further studies when data from analytic tests show the products to be comparable. For a small number of brand products that show small differences in these analytic tests following manufacturing changes, FDA may require additional analytic tests and pharmacokinetic or pharmacodynamic tests to be conducted in animals or humans.

These later studies, PKBPD studies, they are clinical studies in the sense that they are conducted in patients in the clinic, but they are not the large clinical outcome studies commonly used to determine the product's ultimate clinical effects.

These pharmacokinetic and pharmacodynamic studies almost always involve fewer than 100 patients, and in general last weeks, not many months.

Rarely after a brand manufacturing change does the FDA require that a brand company take the last step, repeating a full-scale clinical outcome study. Such studies are not usually necessary because the variability and noise involved in most clinical outcome studies make them inefficient for determining comparability between agents. In fact, of all the hundreds of brand biologic product changes, the vast majority were approved without large clinical outcome trials.

In sum, FDA's scientists and physicians routinely make comparability determinations, since manufacturing changes occur throughout the brand biologic product development and life cycle. The comparability algorithm has existed for over a decade to allow brand biologic manufacturers to change and improve their manufacturing processes.

In closing, I want to emphasize to the Committee again that the science of comparability is not a new ont, but rather an old one used by the Agency and the brand industry for more than a decade to determine comparability.

Chairman Waxman, the Access to Life-Saving Medicines Act will give FDA the authority and the flexibility it needs to ensure the safety and efficacy of biogenerics. I comment you for adopting the same scientific principles, processes, and

procedures that exist for the brand biologic industry when making post-approval manufacturing product changes to the biogeneric sector.

Our mission as a physician reviewer at FDA and that of all my colleagues then an drug now is to protect the public by ensuring the safety of the supply of biopharmaceuticals. No one's interests are served if safety is not viewed as paramount.

Thank you very much.

[Prepared statement of Dr. Schwieterman follows:]

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Chairman WAXMAN. Thank you very much, Dr. Schwieterman.

Ms. Mollerup?

STATEMENT OF INGER MOLLERUP

Ms. MOLLERUP. Chairman Waxman, Ranking Member Davis, members of the Committee, thank you for inviting me to testify today. My name is Inger Mollerup. I am Vice President for Regulatory Affairs of Nova Nordisk, a company with an 80-year history of producing insulin and other proteins.

I am a scientist, not a lawyer, and as such have for the last 30 years been engaged in the design of manufacturing processes and development programs for numerous recombinant proteins. In 2005 I represented the in drug before the European Medicines Agency, the EMEA, discussing the insulin follow-on guidance, and I also presented to the World Health Organization's INN Committee on issues related to naming of all therapeutic proteins, including follow-ons.

Nova Nordisk believes that any pathway for follow-on biologics must be, first and foremost, constructed to protect patient safety, be rooted in the best science, preserve innovation, and respect for proprietary information.

Three major points from my testimony today are:

firstly, that characterization does not tell the whole story; secondly, that pre-clinical and laboratory tests are not sufficient to determine immunogenicity and other important safety parameters; and, thirdly, that current science does not support interchangeability.

Firstly, characterization does not tell the whole story. Any pathway must fully address the patient safety considerations of medicines that are similar to or comparable to instead of same as the reference product. Given that proposals currently before Congress go far beyond the science in an effort to deem products having minor differences in immuno-acid sequence as highly similar, I share with you an experience we had at Nova Nordisk as we were developing a fast-acting insulin analog wherein two potential candidates having one amino acid difference were tested.

All candidates were put into an extensive chemical preclinical and clinical program. The candidate taken to market had only one change to the immuno acid sequence from human insulin, resulting in an analog with significantly shorter timing of action than human insulin and a unique safety profile.

An earlier candidate, which had also one amino acid substitution, showed a positive effect on the timing of action, but in full preclinical animal toxicology studies this dark candidate significantly elevated tumor potential in

rats. Development of this candidate was immediately discontinued.

Even though both analogs were fully characterized, an animal study was required to demonstrate that this seemingly minor difference had enormous consequences for important safety characteristics. Minor differences can have major safety consequences.

Secondly, pre-clinical and laboratory tests are not sufficient to determine immunogenicity and other important safety parameters. Human clinical immunogenicity data must be required, and we have numerous examples illustrating its vital importance.

While developing a complete new process for our insulin analog, we discussed this program with the FDA. FDA stated the no general safety threshold could be applied for new impurities. Even one as low as .1 percent was not acceptable because proteins can be immunogenic at very low concentrations, and it is not known when low is low enough. Immunogenicity data from an appropriate clinical study was, therefore, necessary and included in our submission.

Thirdly, current science does not support interchangeability. Based on today's science, a follow-on biologic cannot be determined to be the same as a innovator drug. For this reason and because of the potential difference in immunogenicity and other drug-specific adverse

events, follow-on biologic products must not be allowed to be interchangeable. The treating physician must at all times be involved in the decision to change from one product to another.

Interchangeability is also not part of the EMEA approval, and Europe has the further requirement that these products are clearly identified to support post-market monitoring.

Nova Nordisk believes that any pathway for follow-on biologics must be, first and foremost, constructed to protect patient safety, be rooted in the best science, preserve innovation, and respect proprietary information.

Thank you for the opportunity to speak here today. Nova Nordisk is ready to assist Congress as this issue moves forward.

[Prepared statement of Ms. Mollerup follows:]

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Chairman WAXMAN. Thank you very much, Ms. Mollerup.

Dr. Venkataraman, we are pleased to have you with us?

STATEMENT OF GANESH VENKATARAMAN

Mr. VENKATARAMAN. Good morning, Chairman Waxman and members of the Committee. I want to thank you for the invitation and opportunity to present to you this morning on this very important topic to our industry and for the general public.

I am Ganesh Venkataraman, Co-Founder and Senior Vice President of Research at Momenta Pharmaceuticals. I am pleased to come before you today to discuss the scientific issues behind the need to create an abbreviated regulatory approval process for generic biologics, which are defined as follow-on protein products in Dr. Woodcock's testimony.

The terms that I use are also defined in the written testimony that we are submitting for the record.

Mr. Chairman, I am a chemical engineer by training, with specific expertise in bioprocess engineering, protein structure characterization, and analytic and quantitative methods for categorizing complex mixtures. While at MIT I, with Dr. Sasisekharan and Dr. Langer developed novel analytic technology that enables characterization of complex mixtures.

With this platform and co-science and leadership at MIT, we founded Momenta. We develop novel drugs and generic versions of complex products. We use cutting edge science to develop affordable and safe generic versions of these products.

Momenta has a strong interest in ensuring that Congress acts this year. We believe our company's experience demonstrates that the science is available today and continues to evolve to enable generic versions of complex mixture drugs.

In my written testimony I focused on five major issues that I will briefly discuss today.

First point, complex biologics can be totally characterized. Not all biologic products are the same, so when we discuss the characterization challenges we must keep in mind the continuum of complexity. Analytic technologies are here today to characterize the less-complex biologics, and approaches like ours and others are actively being developed for those that are more complex.

In my testimony I highlight how our testimony is applied to heparins. While heparins are not biologics, it validates how complex mixtures can be characterized.

The second point is: with such product characterization, generic companies will be able to design and control the manufacturing process to reproducibly make biologic drugs with the same quality as the branded

companies. The manufacturing process for biologic drugs does not occur in random or uncontrolled system. The living cells are highly specialized systems which, in a very careful and controlled manner, produce a final product.

Scientific advances in analytical technologies available to the generic as well as the branded industries allow one to link process parameters to the final product. It is possible and absolutely critical that generic companies build and maintain the same level of process knowledge.

Point three: clinical studies, ranging from small-scale PK to clinical outcome studies, should be used to address any residual uncertainty answering relevant scientific questions. Traditional empirical or full-scale clinical trials must not be a requirement for approval in all cases. While the FDA may require full-scale trials for approval of some biologics, others that have increased level of characterization data should require significantly reduced clinical testing.

We believe FDA is well equipped to work with applicants to determine the degree of testing necessary and define the characterization and trial requirements.

Point four: biologic drugs can be designed to be interchangeable. Interchangeability is an important public health objective and products need to be designed and proved to be interchangeable. It is well within the reach in the near term for a number of products. This can be done through

total characterization and/or through a proper combination of characterization and clinical trials.

Point five: patient safety and product quality will not be jeopardized. We should hole the entire industry, branded and generic, alike, to the highest scientific standards, and allow the expertise of FDA's scientific staff, which will approve and oversee the marketing of innovator and generic biologics.

In closing, Mr. Chairman, there is an opportunity to drive continued scientific innovation by creating a forward-looking, regulated system which balances the respective roles that characterization and clinical data should play. FDA has to be given the opportunity to make the decisions that on comparability which is interchangeability based on the science presented to them. If legislation does not allow for such a pathway today, scientific innovation from technology companies like ours and many others will be stifled, and access to more-affordable choices would be denied.

I hope that my perspectives will be instructive to this debate. I am confident that these efforts under your leadership will be a key contributor to increasing access to safe, effective, and affordable medications to patients in need.

I thank you again for the opportunity to submit

testimony. I look forward to answering any questions.

[Prepared statement of Mr. Venkataraman follows:]

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Chairman WAXMAN. Thank you very much, Dr. Venkataraman.

To begin the questioning, the Chair recognizes Mr. Burton.

Mr. BURTON. I thank the Chair for recognizing me. I have to go put a pharmaceutical in my eye out at the hospital, so I can attest to the necessity for those products.

Mr. Chairman, I am not sure this question should be directed to the panel. It may be directed at you. From everything I have seen, there can be a minor difference in a biological product, and if the pharmaceutical company that created the product in the first place has to give a generic company the information before their patent expires, it seems to me, because of the minor difference that could be created by the generic company, they could apply for a license well before the patent runs out from the original producer. If that were the case, the scientific research being paid for by the original patent company, the pharmaceutical company that developed the product, they could lose their investment after they have created something that is going to be beneficial to everybody.

So my question is: has that been checked out legally and whether or not the originating company can be protected for the duration of their patent?

Chairman WAXMAN. Perhaps we can let one of the panelists

answer it, but it seems to me it becomes a patent question. If the originator of the product has a patent over that product, a minor variation, as you seem to describe it, would not be permitted as a competitor, if it is basically the same product.

Mr. BURTON. I think the bill has a great deal of merit.

Chairman WAXMAN. Which is, of course, by the way, what we do right now with generics and brand name drugs. We allow generics to compete after the patent is over. If there is a new innovation in it or a minor difference, then the FDA would have to decide if it is, in fact, a generic.

Mr. BURTON. I understand that. I like the bill. That is one thing I would like to check out. Thank you, and thank you for yielding.

Chairman WAXMAN. Thank you very much.

The Chair recognizes himself.

Let me address this question to Dr. Gerrard and Dr. Schwieterman. As you testified, for over ten years the FDA health as allowed brand name manufactures of biotech drugs to make changes in the process by which they manufacture their products, but without repeating the original safety and effectiveness trials. This policy seems to me to undercut the brand name industry argument that changes in manufacturing processes can affect safety and effectiveness in ways that could only be assessed through clinical trials.

In your judgment and experience, does permitting companies to make significant manufacturing changes under a comparability protocol, but without repeating clinical trials, adequately protect patients from unsafe or ineffective products?

Ms. GERRARD. I think, as both Dr. Woodcock and Dr. Schwieterman have said, FDA only has one standard for safety and efficacy, so when FDA makes the decision that, after a manufacturing change, that the product is comparable, they have decided that it is going to have the same safety and efficacy as the brand. What we are saying is some of those same principles apply to the development of generic biotech products.

Chairman WAXMAN. Yes.

Mr. SCHWIETERMAN. Yes, let me just add to that. The FDA is a science-based organization. It is filled with scientists. It is filled with physician reviewers. It is filled with people who are expert in data analysis and interpretation. Your question really is one of is the science there to allow in some cases for the absence of clinical trials, and I would say yes, it is there, but you would have to look at the data, you would have to look at the techniques, you would have to look at the actual agent under discussion. You take things on a case-by-case basis, based upon the science and the data, and then make that determination.

Chairman WAXMAN. Are there many examples of products approved under comparability protocols that turned out to have unpredicted safety or effectiveness problems that were only discovered after marketing?

Mr. SCHWIETERMAN. There are none in the U.S. where there were major changes in post-marketing that caused this. We all know the example of Eprex, which occurred post-marketing in Europe. The patients developed PRCA. But the Agency and the biotechnology industry and biopharmaceutical industry in this country has been amazingly good at protecting the public this way.

Chairman WAXMAN. Does the scientific rationale underlying comparability protocols and FDA's ten years of experience implementing it provide evidence that an abbreviated application process for follow-on proteins and biogenerics based on established comparability principles could adequately protect patients from unsafe or ineffective products? Dr. Gerrard?

Ms. GERRARD. I think the comparability policies have been enormously successful from FDA's point, and the American public has benefitted, as well. Brand companies have been able to make manufacturing changes and improve their product without the need to redo clinical trials.

I think we can apply some of those same principles in extending it one step further to generic biotech products.

Mr. SCHWIETERMAN. I would just like to add that I think the rationale is, in fact, one that can be used, coupled with the data, coupled with the case-by-case to develop a safe and effective biogeneric use of the principles we outlined.

Chairman WAXMAN. Dr. Schwieterman, Ms. Mollerup testified that immunogenicity can arise so unpredictably from changes in biologics that a follow-on biologic will always require a clinical trial to assess immunogenicity. When a brand name company uses the FDA's comparability guidance to make changes to its existing biologic products, are clinical trials always required to demonstrate that no new immunogenicity concerns have arisen?

Mr. SCHWIETERMAN. Always is an absolute, and absolutes are only things that can be supported by the data. FDA is a scientific organization, and I would say that no. In every instance ought there be a clinical trial for immunogenicity? No. It would depend upon the nature of the case. It would depend on the data that are there. And I think there are ways and methods for sure beyond clinical trials to determine immunogenicity. In fact, clinical trials, themselves, have limitations in this regard, as they do with other infrequent safety AEs.

Chairman WAXMAN. Should there be more concern about immunogenicity for follow-on proteins than for brand name proteins?

Mr. SCHWIETERMAN. I don't think there should be more or less concern about immunogenicity. I think that the safety of all agents, particularly biogenerics and biopharmaceuticals in this country is a critical issue for the FDA. I think that the same standards, the same kinds of oversight, the same considerations for biogenerics ought to apply for them as to do for present-day biopharmaceuticals.

Chairman WAXMAN. Let me ask a question of Dr. Venkataraman and Dr. Allan. A number of companies have expressed doubts about whether copies of biotech drugs can be made safely. They have suggested that the manufacturing process for producing these drugs is so complex that new companies will not understand biologics manufacturing well enough to produce safe versions of these products. Isn't it true that there are a number of companies who already make brand name biotech drugs, either for themselves or on contract for other companies, who would be likely to want to make copies for biotech drugs if there were a legal pathway?

Mr. ALLAN. I believe there are contract manufacturing organizations that do make branded products, either at the research level, the development stage level, or even at the commercial level.

Chairman WAXMAN. Yes.

Mr. VENKATARAMAN. I would like to add I think the brand manufacturers sometimes have made the process to be a black

box. I think the science is there now to be able to go back and decouple product and relationship to the process so that you could use a different cell line and come up with a different process that would ultimately provide you the same end product. Provided you couple that with the characterization of looking at process-related impurities and end product, you could get there to the same level of being in a brand manufacturer.

Chairman WAXMAN. Thank you very much.

Mr. Davis?

Mr. DAVIS OF VIRGINIA. Thank you, Mr. Waxman.

Ms. Mollerup, let me start with you. The generic system we created for pharmaceutical drugs in 1984, which bears Mr. Waxman's name, balanced and abbreviated approval systems for generic drugs with patent restoration and new exclusivity for innovators. Doesn't such a critical balance continue to stimulate the development of new cures for drugs, having that balance?

Ms. MOLLERUP. In my mind it is important that we keep the balance that will still foster innovation, and as this process goes forward towards defining a legislative and regulatory system, that that is acknowledged, because you would still want new drugs to come on the market in this country.

Mr. DAVIS OF VIRGINIA. What kind of impact would a

system that fails to assure safety or sustain innovator intellectual property rights have on innovation?

Ms. MOLLERUP. A system that would fail to protect safety I think would be detrimental for both innovation and follow-on manufactures, and obviously first and foremost for public health. I think it is very important, as Congress moves forward, that the pathway you are moving towards is really constructed to protect patient safety and be rooted in the best science, and there is a lot of strong and good science available for this.

Mr. DAVIS OF VIRGINIA. The FDA stated in its testimony that demonstrating the similarity of a follow-on protein product to a reference product is more complex and would require new data. I guess my question is: does this mean FDA should require clinical safety data for follow-on biologics, or do you think there are cases where they could make the determination it wouldn't?

Ms. MOLLERUP. Based on my experience with those complete second-generation processes that we have developed and are developing at Nova Nordisk, these require immunogenicity data in all cases for the simpler ones like insulin, described in my testimony. Besides that, PKPD was required to assess both pharmacokinetics and efficacy for a more complex one like a co-correlation factor, substantial clinical data will be required, as well as immunogenicity.

So, based on the experience that we have with processes that are less substantial in the change that they involve than doing a follow-on, from my standpoint, where the science is today, immunogenicity trials will always be required.

Mr. DAVIS OF VIRGINIA. Thank you.

Let me ask Dr. Venkataraman and Dr. Allan, you are both from small biotech companies. FDA stated in their testimony that technology is today not yet sufficient to allow for comparisons of complex protein products. Do you agree with that?

Mr. ALLAN. Well, it has to be viewed on a case-by-case basis. I think for the product we developed the analytical methodology that we used, which was fairly extensive, was very adequate to demonstrate the structural characterization of the property.

Mr. DAVIS OF VIRGINIA. DO you think it depends?

Mr. ALLAN. It will depend on the products. There are some proteins that are fairly simple, relatively speaking, and you can characterize them extremely well.

Mr. VENKATARAMAN. I agree. I think on a case-by-case basis there are several proteins that can be characterized well today, and science continues to evolve. Academic groups and other companies I know are working very actively towards creating novel technologies to be able to do this for more complicated products. And I think a regulatory and a legal

legislative incentive is going to propel that technology forward much faster to be able to do this much more sophisticatedly.

Mr. DAVIS OF VIRGINIA. How close are we, do you think? It is hard to say, I know, but a couple years, ten years?

Mr. VENKATARAMAN. It is difficult to say, but four years ago, when we started working on the program that we were, people thought it was impossible to do. We were discouraged extremely. Today we have an application, we have talked to the FDA. It has been completely solved. I think similar situations have been reported by other people. So it is a matter of providing the right incentives for the scientists to be able to take it on.

Mr. DAVIS OF VIRGINIA. Okay. Are there any non-clinical tests or technologies that could fully substitute for studying the safety of biotech products in humans?

Mr. VENKATARAMAN. I would say that the safety, per se, so the comparability of the two products, characterization becomes a very important aspect of knowing how close you are to the innovator product. I think there are multiple analytical techniques that provide you very rigorous estimation of the product quality and product attributes, so yes.

Mr. DAVIS OF VIRGINIA. All right.

Let me ask Dr. Schwieterman and Ms. Gerrard, the FDA

highlighted in its testimony the importance of ensuring that facilitating the development of follow-on product through abbreviated pathways doesn't discourage innovation and the development of new biological products. They also refer to the Hatch-Waxman Act as a balanced approach. Do you think an extension of data exclusivity period and certain patent protections would help encourage innovation and development with biological products?

Ms. GERRARD. I am not a lawyer. I am a scientist. I guess I have confidence in the innovation biotech companies that I work with to continually come up with new and better products.

Mr. DAVIS OF VIRGINIA. All right. From a scientific point of view it is achievable, but from a policy point of view you are going to take a pass on it?

Ms. GERRARD. I am not a lawyer. I am a scientist.

Mr. DAVIS OF VIRGINIA. That is fine.

Mr. SCHWIETERMAN. I will take a pass, as well. I am a physician scientist. From a scientific point of view I agree with what Dr. Gerrard said.

Mr. DAVIS OF VIRGINIA. Well, Henry and I are both lawyers. Thank you.

Chairman WAXMAN. Thank you, Mr. Davis.

Mr. Yarmuth?

Mr. YARMUTH. Thank you, Mr. Chairman.

As a child I was left way behind on science, so I am going to pass on the science questions for a minute and ask something I know a little bit more about, and that is the business side of this, and I am asking business questions of a panel of scientists. I understand that.

Am I correct in assuming--and anyone can answer this--I take it, just reading between the lines, we have several representatives from generic manufacturing companies and one from a brand name company. Judging from what we have heard about the complexity of these biologic drugs as opposed to chemical-based drugs, and we all know the stories about how chemical-based drugs cost pennies apiece to produce and they are sold for whatever, but it seems to me that the economics of biologics are significantly different and more complex and therefore dramatically more expensive. If I am correct in that assumption and the process is inherently expensive, how much money can we save by producing them on the generic basis or follow-on basis as opposed to the brand name?

I guess a premise, we know that for Claritin and for Zantac and all these other products, and many of the discuss that are actually still by prescription, that we have a significant amount spent for advertising and marketing. I assume marketing, anyway, is still a big component of the biologics business. But what are we talking about, either from a historical perspective that you know about or

potentially that we are talking about saving by allowing these drugs to be produced generically?

Mr. ALLAN. I can give that a shot. Actually, I don't think anybody around this table is from the generic industry. Some of us are from the innovation biotechnology industry.

With regard to price, it is going to be a case-by-case basis. There is no doubt to make a complex protein is more expensive to make a small molecule. The manufacturing facilities that are needed, the overhead, so to speak, that goes into the whole program is probably larger than the financial commitment you would want to make for a small molecule plant. So I think intrinsically it is a more expensive business, but I believe that, you know, certainly none of us would be sitting around this table if we felt that we couldn't make these types of products at a significant price reduction to the innovator product. It will be a case-by-case. What would be the percentage reduction I don't think we could--I certainly would not comment on that right now, but, as I said, it will be less expensive.

Mr. YARMUTH. Go ahead.

Mr. VENKATARAMAN. I was just going to add one comment. I don't know if I can give you any numbers, but what I do know is that the margins between the cost to manufacture to the actual price are significant. I don't have exact numbers, but it is quite significant, and I assume that that could

translate into cost savings in the long run.

Mr. YARMUTH. Again, I understand I am asking business questions of scientists, but would the savings result, assuming that we allow an easier pathway to producing generics, would the savings result more from the competitive aspect, or would they result from the fact that, just because we have protected the brand name manufacturer, that we have allowed that price to be very, very high, and that just by eliminating the exclusive we bring the price down? Would the savings be inherent? Would they be related to competition, or is it just because we are allowing exorbitant profits now, understanding that those profits are being allowed to allow the company to recover some of its investment?

Mr. ALLAN. I think it will be the introduction of competition, to a certain extent.

Ms. GERRARD. And my economic knowledge might be right behind my legal knowledge, but I think what we have to understand is that, while biologics might be more expensive to make than drugs, that there is still a huge margin there, and that, while the cost savings, even conservative estimates that say 25 percent, which we have seen, when you consider that the cost of a biologic is so high that a 25 percent savings is a huge amount.

Mr. YARMUTH. You look like you want to answer.

Mr. VENKATARAMAN. The pricing for a drug that a company

like Momenta would launch as a generic would be lower by at least 20, 25, 15, depends on the dynamics, but because the lower prices of the drug I think the cost saving would be achieved.

Mr. YARMUTH. Ms. Mollerup, did you want to comment?

Ms. MOLLERUP. Yes. I mean, cost is an important consideration and I think that lower cost of drugs is good, as long as it is not at the expense of patient safety. I guess, again, back to the need for clinical trials, I would like to share with you, which I guess indicates somewhat where the borderline may be. In Europe we have not only had two approvals of follow-ons, but also one rejection. That was on an Interferon Alpha that did not show comparability in its clinical trial in that more patients had relapse of their disease after the treatment with Alferon was stopped, compared to the reference product, and there were also more side effects in the Alferon group. Again, I am neither an economist. I am also a scientist, but it just goes back to the equation of cost savings, that some cost savings can be realized but the products are expensive to produce, and as this example from Europe shows, care really has to be exercised as to make sure that the appropriate comparable clinical data, not a copy of the original data set that was handed in, but appropriate comparable data ensuring comparable efficacy and safety is included.

Mr. YARMUTH. Thank you.

Chairman WAXMAN. Thank you, Mr. Yarmuth.

Mr. Welch?

Mr. WELCH. Thank you, Mr. Chairman.

Dr. Gerrard, Dr. Mollerup argued that the risk of immunogenicity from a follow-on product must always be evaluated with clinical trials. That is my understanding of her testimony. In your view, are clinical trials the best or the most sensitive method of detecting this?

Ms. GERRARD. Not always. I think we have to keep in mind that immunogenicity, as I stated, a product having greater immunogenicity really is not an issue; it is when there are clinical consequences. Immunogenicity just means you make antibodies to the product. Most of the time they are not neutralizing. Many times they are temporary. Patients continue to be treated. So it is not always an issue.

Second, is clinical trial the best way to determine immunogenicity differences between two products? It may not always be the case. Sometimes more rigorous analytical comparisons, either assessment of the product and instability are really a much more sensitive way of determining whether that product is going to cause problems.

Mr. WELCH. Thank you.

Dr. Schwieterman, would you agree with that?

Mr. SCHWIETERMAN. Yes, I would. I think the concept of immunogenicity is one that has been talked about a lot, but, in fact, it is a quite complex subject. There are certain kinds of immunogenicities, then there are other kinds. We have had many day-long conferences about this. The ability of clinical trials to detect immunogenicity depends on what you are talking about. For most of the things that have been bandied about, actually clinical trials are rather poor measures for picking up the kinds of outcomes that you have heard.

Mr. WELCH. Thank you.

I would ask this question to both of you, as well. Proponents of the generic biological pathway, as you know, always raise the example of Eprex, Johnson & Johnson's European version of Epogen. Can you explain a little bit about what happened with Eprex? I will start, I guess, with you, Dr. Schwieterman.

Mr. SCHWIETERMAN. I don't know, of course, the data on the manufacturing changes that were made, nor was I privy to the investigations made. I know that Johnson & Johnson underwent a great deal of investigations. I mean, just to tell the story as I know from my standpoint, Eprex, which was one of the erythropoietin--ESAs, they are called, in general, erythropoietic stimulating agents--was marketed and approved overseas, and then cases of autoimmune disease or a very bad

autoimmune immunogenic reaction to the drug, itself, ensued. In other words, the body started reacting to its own protein based upon that.

The thing about this particular case that is different is that, number one, it occurred overseas, so, you know, there was no real knowledge of whether the analytic tests that were performed there were adequate or complete and whether they would have been picked up at the FDA.

Number two, the ultimate investigation into this product, as I understand it from Dr. Segal's testimony several weeks ago, picked up on impurities that are actually determined with analytic tests after the fact, and most of the investigation ensued upon that; that is to say, the actual analysis of the product, itself.

From my vantage point, it is clearly an important issue, because we need to understand it, but it doesn't visciate, it doesn't make the arguments about analytic tests weaker, in my estimation. In some ways it makes them stronger.

Mr. WELCH. Go ahead, Dr. Gerrard.

Ms. GERRARD. I was just going to add to that. Pure red cell pledget is a very serious disease, but it occurred in 1 in 10,000 patients. So could this have been detected in a typical clinical trial of, say, several hundred people? No, it could not. What actually did resolve the issue for J&J's Eprex was a more rigorous analytical characterization to

resolve that problem.

Mr. WELCH. Thank you. How large a clinical trial would have been required to identify that side effect?

Ms. MOLLERUP. I think that everyone agrees it would have taken an extremely large clinical trial, and, from my perspective, the purpose of doing these comparative immunogenicity trials where you can, from the blood samples, isolate antibodies, characterize them, find out whether they are benign or not, and I fully agree with Dr. Gerrard that not all antibody responses are a safety issue.

But with the case of these comparable clinical trials to test immunogenicity, the real important point here is that such trials can tell us if there is a major problem. For innovator products, as well as for follow-ons, it is the long-term safety monitoring that is also needed in order to pick up on minor problems like this.

Mr. WELCH. How large a clinical trial would have been required, then, Ms. Mollerup?

Ms. MOLLERUP. I don't have the clinical for Eprex because I don't have that statistic, but, back to Dr. Segal's testimony, it would take a study of about 50,000 patients to have a good chance of detecting a serious effect in a patient, 1 patient out of 1,000. But I don't have the statistics on Eprex.

Mr. WELCH. And my understanding--anybody can answer

this--is that J&J, itself, doesn't argue that the Eprex problem would have been avoided, in fact, had they conducted a clinical trial before marketing the change product. Dr. Gerrard?

Ms. GERRARD. No, they would not have detected it in a clinical trial. Every product is subject to post-marketing surveillance.

Mr. WELCH. Right.

Ms. GERRARD. So a very rigorous post-marketing surveillance program is also important for every product.

Mr. WELCH. Dr. Schwieterman?

Mr. SCHWIETERMAN. One point I want to make is you don't conduct clinical trials for no reason. You are exposing patients to agents and putting them through a rigamorole and data collection and blood drawing and so forth to collect scientific data for scientific reasons that are pre-established in hypotheses, and so to argue that clinical trials should be conducted all the time is really to negate the basic premise of a clinical trial, which is the study of question.

In the case of Eprex, it would have been an impossibly large study to have studied that particular issue; therefore, a clinical trial not only would have been undetected, insensitive to that particular change; it wouldn't have offered any information at all.

Mr. WELCH. Just following on your point, would it make scientific sense to argue that the express example supports a clinical trial requirement for follow-on products but does not support that same requirement for brand name products?

Ms. MOLLERUP. I think, from looking at what is required for the branded industry, I mean, the trials that we undertake, both phase two and phase three trials, immunogenicity is an obvious part of that program, because we are working with proteins and the immunogenetic profile of our products are also not established as we take them through the clinical program, so that is certainly part of the testing we do, as well.

Mr. WELCH. I'm not sure I understand you. You are saying that you have to have those clinical tests for the follow-on products but you don't have to have them for the brand name products?

Ms. MOLLERUP. No. I am saying the exact opposite. I am saying that we, in the brand products in the clinical trials that we use to take these to the market, immunogenicity studies is an integrated component, and what we find reasonable to establish clinical comparability for the follow-ons is to also study immunogenicity in an appropriately sized comparative trial, and that will be a lot smaller than the innovator phase three studies.

Mr. WELCH. Dr. Schwieterman, go ahead.

Mr. SCHWIETERMAN. I guess I would disagree with that. Mandated clinical trials to study immunogenicity is not something that is scientific, but rather political. In this particular case, if the science are there, depending upon the drug, depending upon the question, the patient, and the test, you could do a clinical study in certain instances where you believed that information would be useful from that clinical study. But to mandate it for all studies would be to also perform it for those cases where it wouldn't be useful.

I think that what ought to happen is that the FDA, like they do now, be able to have the flexibility and the authority to use their assessments of the data and the context of that data to make judgments about the need for further clinical studies.

Mr. WELCH. Thank you.

Dr. Gerrard, last word?

Ms. GERRARD. I will just add to that. I think FDA does need that flexibility. You look at the history of the product, have there been any clinical consequences to the immunogenicity? What about the analytical characterization? You look at the whole picture. If there are remaining questions, of course safety is paramount. We want FDA to have the ability to request any additional data that they need to make sure that that is a safe product.

Mr. WELCH. Thank you. I yield the balance of my time.

Chairman WAXMAN. Thank you very much, Mr. Welch.

Dr. Mollerup, would you support giving FDA the ability to require and enforce post-market studies for both the generic and for the brand name drugs?

Ms. MOLLERUP. I am from Europe, so I have a fair amount of knowledge of the regulatory system here in the U.S., but may not be accurate on all the details. From my perspective, the FDA should be able to put the same requirements to both innovators and follow-ons, because same safety issues are involved.

Chairman WAXMAN. Right. In the United States the manufacturer agrees when the product is licensed to do follow-up tests for post-marketing, but they may not do it because there is not a sanction except to take them off the market, which has never been used. Do you think FDA should have the power to require post-marketing safety studies? You say it should be for both or either when it is necessary. Do you think FDA ought to have that power?

Ms. MOLLERUP. The power not only to ask for the data, but also actually to get it?

Chairman WAXMAN. And to insist it be done?

Ms. MOLLERUP. Yes, I think they should.

Chairman WAXMAN. Thank you.

Well, I thank all of you very much. You have been very helpful, and I appreciate your testimony. This may be

self-serving, but the bill does allow FDA to require clinical trials. It allows FDA to do whatever is necessary to determine that the science indicates a generic version is safe and effective.

Thank you very much.

I want to call forward the witnesses for our third panel.

Yvonne Brown is an individual living with multiple sclerosis and is speaking today on behalf of the National Multiple Sclerosis Society.

Mary Nathan is an individual living with a rare disease called Gaucher Disease, and is speaking today on behalf of the National Organization for Rare Disorders.

Nelda Barnett is a Board Member for AARP.

Priya Mathur is the Vice Chair of Health Benefits, Board of Administration, at the California Public Employees' Retirement System, CalPERS.

Scott McKibbin is the Special Advocate for Prescription Drugs for the State of Illinois.

Dr. Henry Grabowski is a Professor of Economics and the Director of the Program in Pharmaceuticals and Health Economics at Duke University.

Jonah Houts is a Senior Analyst at Express Scripts, Inc., a pharmacy benefit management company, PBM, representing 1,600 clients, including large, self-insured

employers, government payers, union, and health insurance companies, and covering more than 50 million people.

We welcome you all to this hearing today. Your prepared statements will be in the record in full. We would like to ask each of you to limit the oral presentation to around five minutes.

It is the custom of this Committee, as you have already observed, having sat through the earlier panels, to ask all of the witnesses to be sworn in, so I would like to ask each of you to rise and raise your right hand.

[witnesses sworn.]

Chairman WAXMAN. The record will indicate that each of the witnesses answered in the affirmative.

Ms. Brown, why don't we start with you, if you have the microphone passed over.

The timer, by the way, will be green, and then it will turn to yellow for the last full minute, and then red when that last minute is up.

Thank you so much for being here.

STATEMENTS OF YVONNE BROWN, FOR THE NATIONAL MULTIPLE SCLEROSIS SOCIETY; MARY NATHAN, FOR THE NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD); NELDA BARNETT, BOARD MEMBER, AARP; PRIYA MATHUR, VICE CHAIR, HEALTH BENEFITS-BOARD OF ADMINISTRATION, CALIFORNIA PUBLIC EMPLOYEES' RETIREMENT SYSTEM (CALPERS); SCOTT D. MC KIBBIN, SPECIAL ADVOCATE FOR PRESCRIPTION DRUGS, STATE OF ILLINOIS; HENRY GRABOWSKI, PH.D, PROFESSOR OF ECONOMICS, DIRECTOR, PROGRAM IN PHARMACEUTICALS AND HEALTH ECONOMICS, DUKE UNIVERSITY; AND JONAH HOUTS, SENIOR ANALYST, EXPRESS SCRIPTS, INC.

STATEMENT OF YVONNE BROWN

Ms. BROWN. Thank you, Chairman Waxman and distinguished members of the Committee, for inviting me to provide testimony at this hearing, and thank you, Chairman Waxman, for your leadership on this issue.

My name is Yvonne Brown. I live in Waldorf, Maryland. I have multiple sclerosis, or MS. I am not a pharmaceutical company. I am not a lobbyist. I am simply a 44-year-old woman who struggles every day with the devastating effects of MS and the unaffordable cost of treatment.

MS is chronic, it is unpredictable, often disabling disease of the central nervous system. It basically stops

people from moving in one way or another. There is no cure. MS causes loss of coordination, memory, extreme fatigue, paralysis, blindness, and many other symptoms. These problems can be permanent or they can come and go.

More than 400,000 Americans have MS, and every hour someone is newly diagnosed. The National Multiple Sclerosis Society recommends treatment with one of the FDA approved disease modifying drugs to lessen the frequency and severity of attacks and to help slow the progression of disability. Unfortunately, the cost is often financially devastating. I know this personally.

Four of the six FDA approved disease modifying drugs are considered biological drugs. They range from $16,000 to $25,000 a year. That is about twice the amount of Social Security disability I receive annually. For me, sometimes the financial struggle to get my treatment can be troubling, more troubling than this incurable disease.

I am here today to appeal to the Committee. My personal story is an example of the immediate need for this legislation that Chairman Waxman has introduced.

In the past I have struggled a lot with my MS and with trying to get the prescriptions I need to feel a little better. I was diagnosed with MS in April of 2000 at 37 years old. In August, 2000, I was prescribed Avonex, a biological drug from Biogen. The cost of Avonex is high, and I did

whatever I could to afford my prescribed therapy. I sold my computer, I disconnected my phone, I skipped paying a lot of my bills. Despite this, I lost my home before the end of 2001 and I was living in my car. From 2001 to 2005 I was homeless.

I struggled for years to get approval from Social Security and I tried for over three years to be approved for subsidized housing. I was even turned down for help at shelters because of my MS. The staff there felt that I was a health liability due to my problems with balance and frequent falls. I became accustomed to begging, borrowing, and pleading for any help so I could get treatment.

Unfortunately, access to my treatment was sporadic and I paid the consequences with increased symptoms and more frequent attacks. It was a terrible cycle. As a result of not having access to Avonex for an extended period of time in 2004 I was hospitalized. The cost of my 24 hour hospital stay was nearly $1,000. I am still trying to pay that bill.

Today, after finally being approved for Social Security disability, I receive $1,100 a month, and I am covered under Medicare. I have coverage for my medications, but my co-payment is $220 a month just for Avonex. When you only have $1,100 a month to live on, $220 might as well be $220 million.

I don't want to be homeless or live in my car again, so

I cannot miss rent. I don't want to risk my health, so I cannot skip too many meals. I often skip paying bills, but I cannot get too far behind or risk losing my electricity or other vital services. And I do my best to pay my share to those who provide my treatments. Even today I must miss my treatments occasionally. There is simply nothing I can do sometimes.

It is a misconception that help is readily available. Existing programs are often difficult to navigate, have varying criteria, take a long time, and sometimes run out of money. For example, last year I was finally approved for assistance by the National Organization for Rare Disorders. Before I received my assistance they ran out of funding. It was also possible to get assistance sometimes from Biogeniodec. After asking them for help over a year ago, I think I am close to getting help with coverage during the Medicare part D donut hole, which I will already enter in April. I learned my lesson, though. This time I know not to count my chickens before they hatch.

As a person with MS, I take other prescription drugs for hypertension, depression, and several supplements. The difference is that the generics are available. This keeps my co-payments low and manageable. Most importantly, I do not have to miss these treatments because I cannot afford them. But this is not true for my MS therapies and never will be

unless something changes.

Hopefully you can help with a solution. I am a person with a chronic, life-long, costly disease, but I want to stay out of a wheelchair, I want to stay out of the hospital, I want to contribute my talents to the community, I want to pay my taxes, I want to be healthy so I am able to help others who have MS. I want to stay on my treatment. If I don't have access to treatments, my health will decline.

The stress from the story I have told you, which I live with, has caused me to begin to lose my hair. Frankly, I don't really care. I just want to battle this beast that is trying to take away my movement.

My story is not unique. Millions rely on biologic drugs. Millions struggle terribly with the cost. If I can leave this Committee with one thought, it is that no matter how good a drug is supposed to be, it has not chance of being effective if it is not affordable to those who need it.

For a long time no treatments were available for MS. Now there are. The sad thing is it doesn't matter. Some people just can't afford them. The cost is too much. We have to change that. This legislation has the power to move us a little closer. We all know that providing more affordable medications for all Americans is a serious priority. For biologic MS therapies, we will never, ever reach that goal if we don't start by simply providing the

pathway. It is a necessary first step.

Thank you again for your invitation and attention. I hope you remember me and people like me as you consider this legislation. Please help provide more affordable biological drugs for those who desperately need them. Help establish a regulatory pathway for the FDA to review and approve follow-on biological therapies.

Thank you.

[Prepared statement of Ms. Brown follows:]

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Chairman WAXMAN. Thank you very much, Ms. Brown.

Ms. Nathan.

STATEMENT OF MARY NATHAN

Ms. NATHAN. Mr. Chairman and distinguished members of the Committee, I want to thank you for the opportunity to testify before you today. My name is Mary Nathan, and I am affected by Gaucher disease.

As one of 4,800 people being treated worldwide with Cerezyem, I understand, in a very practical way, what it means to be alive because of a recombinant biological medicine. I also understand what happens when the cost of a life-saving drug is unaffordable.

Gaucher disease is a rare genetic disorder classified into three categories and characterized by the deficiency of an enzyme necessary to break down fats called glycolipids. Because the enzyme is in short supply, lipids collect in the spleen, liver, bone marrow, and other organs. Left unchecked, the accumulation of lipids causes problems such as anemia, bleeding, organ dysfunction, and abdominal enlargement, deterioration of the joints and bones, breathing problems, fatigue, and reduced ability to fight common infections. Type I is the most common. It strikes 1 in

40,000 people in the general population, and 1 in 600 Jews of Eastern European origin.

When I was diagnosed in 1966 at the age of 11, very little was known about Gaucher Disease. Given the increased size of my spleen and my low blood count, doctors scheduled me for a splenectomy within weeks of my diagnosis. Shortly after that I was hospitalized with a high fever, excruciating pain, and an inability to walk. We learned later that lipids had migrated quickly to my bones, since the doctors had removed my spleen. We also learned that I had experienced a Gaucher bone crisis, a painful episode that would repeat often as my disease progressed.

By the time I entered college there was little doubt that I had a severe form of what is known as Type I Gaucher Disease. At the age of 23 I underwent orthopedic surgery to straighten my leg and replace my destroyed hip. After a long recovery I was able to walk without pain for the first time in years. This respite lasted until 1988, when the implanted prosthesis became painful and unstable, so again I underwent surgery and began to experience complications that left me fighting for my life.

My red blood cell count was dangerously low due to a reaction, depriving my bones of oxygen. I then began to experience an ongoing cascade of bone infarcts, vertebrae fractures, and a serious fracture of my other hip.

To head off further damage, my doctor suggested a surgery of last resort known as a girdlestone procedure to repair my hip. Few patients ever walk again after this procedure.

What happened next marked a historic medical breakthrough that would change the course of my life and my disease. After 30 years of intensive scientific research, scientists at the National Institutes of Health discovered a treatment for Gaucher Disease, and in April, 1991, the Food and Drug Administration approved a commercial version called Ceredase.

After three years of enzyme replacement therapy, my overall health improved to a point where reconstructive hip surgery was possible. In November, 1994, after seven years in a wheelchair, I took my first real steps.

There is no question in my mind that I am alive today because of the orphan drug Ceredase. What concerns many of us, however, is that the miracle drug is priced out of the reach of individuals, and thus poses unprecedented challenges for patients who need the drug, for the doctors who treat us, for employers struggling with the high cost of health insurance, and for insurers and Government programs helping to pay our medical bills.

In 1994 most patients were converted to Cerezyme, the Genzyme Corporation's newly approved orphan drug, to replace

Ceredase. The cost of Cerezyme differs from patient to patient because dosages are based on body weight. My dosing regimen is 60 units per kilogram of body weight for infusion. At 130 pounds, my treatment runs about $12,600 per administration, or about $300,000 a year for 24 doses. An additional $25,000 in cost is added for administering the drug and testing and monitoring my response and overall health. This brings the cost for all charges related to my treatment to over $328,000 a year. Now, over a 16-year period since its approval in 1991, I estimate that the payments for my drug have reached well over $4.5 million.

In conclusion, the wave of the future in medicine is biotechnology to treat rare diseases like mine and those diseases affecting wider populations. There is no reason why biogenerics cannot take their rightful place in America's marketplace alongside generic drugs.

Based on some estimates, it is said that biogenerics could save between 10 percent and 20 percent. If that holds true, millions of dollars could be saved annually just for the 4,800 patients currently on Cerezyme.

Mr. Chairman, I want to thank you personally for introducing your legislation. It is time to make safe and effective life-saving biotech therapies accessible and affordable to the millions who need them.

The Access to Life-Saving Medicines Act will create

competition in the marketplace and, in turn, foster innovation. Hopefully a balance will be struck that encourages innovation yet allows more affordable follow-on biologics to come to the marketplace.

Thank you for your time and attention to my testimony.

[Prepared statement of Ms. Nathan follows:]

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Chairman WAXMAN. Thank you very much, Ms. Nathan.

Ms. Barnett?

Ms. NATHAN. You are welcome.

STATEMENT OF NELDA BARNETT

Ms. BARNETT. Mr. Chairman and members of the Committee, I am Nelda Barnett of AARP's Board of Directors. AARP appreciates the opportunity to testify in support of creating a pathway for generic biologics.

AARP has endorsed the Access to Life-Saving Medicine Act because we believe this legislation will enable the FDA to establish a process for the approval of safe, comparable, and interchangeable versions of biologics. We call on Congress to pass the legislation this year.

Biologics are used every day to treat serious diseases such as cancer, multiple sclerosis, anemia, and rheumatoid arthritis. While biologics hold great promise for treating some of the most serious diseases, these treatments can be expensive, costing tens and hundreds of thousands of dollars. Some people are fortunate enough to have insurance coverage or the means to be able to afford these medications, but many are not so lucky.

Nothing illustrates how important it is that we have a

pathway to lower-cost generic versions than the stories of millions of Americans who currently cannot afford a high-priced biologic drugs, such as we have just heard.

My colleague on AARP's board of directors, Bonnie Cramer, could not be here today, but she has asked that I share with you one particular story. Bonnie suffers from severe rheumatoid arthritis, and over the years has undergone a variety of treatment options, including a biologic drug, Enbrel, which has helped her. Bonnie has encountered many people who suffer from her condition who are not able to afford medication. One particular woman was so affected by the disease that her fingers were gnarled and she had difficulty walking and used all of her energy just to get through the day. This woman recounted how she was trying to find a way to get access to Enbrel but could not due to the high cost of the drug.

Bonnie tells it best in her own words. She says, ''Having lived with this disease for 40 years, I know how incapacitating it can be and how the pain can be unbearable. I know what hope biologics can give to someone whose life is affected. To know that it cannot be obtained by other people with deadly diseases is brutal. How do you tell someone that they cannot have a treatment that may alter their lives significantly?''

The astronomical cost of these drugs not only impacts

consumers, but also health care payers such as employers, private health care plans, public programs such as Medicare and Medicaid. One way to control these costs is to provide a pathway for the approval of generic versions of these drugs. Any prescription drug therapy treatment must be affordable and safe in order to be effective for individuals. H.R. 1038 leaves the scientific determinations up to those who are best equipped to address them, the FDA. Common sense, alone, tell us that this agency has the scientific knowledge to approve the brand name biologics, surely has the ability to provide a pathway for generic approval of the same biologic.

The Hatch-Waxman Act created a pathway for FDA to approve generic prescription drugs. Twenty-three years later the time has come for generic approval of biologics. H.R. 1038 provides FDA the authority to produce the safe, comparable, or interchangeable version of the biologic. Our members and all Americans need Congress to enact this bipartisan legislation this year. We are pleased to see this Committee and Members from both Houses of Congress and both sides of the aisle moving forward on this issue.

Thank you again for inviting us here. I am happy to answer any questions.

[Prepared statement of Ms. Barnett follows:]

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Chairman WAXMAN. Thank you very much, Ms. Barnett.

Ms. Mathur?

STATEMENT OF PRIYA MATHUR

Ms. MATHUR. Good afternoon. Mr. Chairman and members of the Committee, I commend you for convening today's hearing and for the introduction of bipartisan legislation to enable consumer petition in the biopharmaceutical marketplace.

On behalf of the California Public Employees' Retirement System, or CalPERS, I welcome the opportunity to testify about this issue of importance to our members, to our State, and to our Nation.

Let me begin by introducing myself and CalPERS. My name is Priya Mathur, and I was elected by 400,000 public sector employees to serve on the board of CalPERS, to invest their $230 billion of retirement assets, and to manage their multi-billion-dollar health care program.

CalPERS' health program covers 1.2 million active and retired public employees and their families. Notably, CalPERS is the third-largest purchaser of employee benefits in the Nation, behind only the Federal Government and General Motors, and it is the largest purchaser of health benefits in California.

This year CalPERS will spend almost $5 billion on health benefits, or $13.4 million per day. Of that amount, CalPERS, for the first time, will spend over $1 billion on members' prescription drugs. At a time when our State is trying to expand health insurance coverage to more Californians, slow the rate of growth in health care costs, and make our health care system more efficient, the high cost of biopharmaceutical products presents an unsustainable challenge to calPERS and to our entire health care system.

CalPERS has long been a leader in implementing cost effective health care programs. Among many strategies, we have instituted innovation prescription drug benefit cost-sharing designs to maximize the use of generics and therapeutically appropriate brand drugs. CalPERS has actually achieved tremendous success in controlling prescription drug costs through the use of generics. This has been possible thanks to the chairman, whose efforts two decades ago led to the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984, what we call Waxman-Hatch.

As you well know, Waxman-Hatch gave the FDA the authority to provide an abbreviated approval process for those products deemed equivalent to an innovator product after patent expiration. Without generic substitution, we estimate that our costs would be about 60 percent higher than

they are today. Generics save our enrollees and our State taxpayers hundreds of millions of dollars every year.

In spite of all of our cost containment efforts, CalPERS has seen an average annual increase of about 13.5 percent for our HMO and PPO products since 2002.

Mr. Chairman, CalPERS' spending for biotech products is distressingly substantial and rising at a rate that is significantly higher than traditional pharmaceuticals. Because of the complex delivery requirements of many biopharmaceuticals, it is exceedingly difficult to break out a stand-alone spending line for these products. However, we believe that our spending on so-called specialty drugs is a good proxy, because biotech products make up the great majority of spending in the specialty drug category.

Total spending for specialty drugs was $83.7 million in 2006, a one-year increase of 16.9 percent, compared to a 5.4 percent increase in traditional prescription drugs. On average, spending for biotech products was at least $55 per day, compared to traditional drugs at only $2 per day.

CalPERS supports a competitive health care marketplace that leads to innovation and life-saving medicines; however, competition does not exist today because the FDA asserts that it does not have the authority to approve biogeneric products. As a result, today's biotech companies are benefitting long after patents expire and are profiting at

the expense of all Americans.

CalPERS supports giving the FDA explicit authority to approve biogeneric products that are safe. Without the ability to access less-expensive comparable and interchangeable biopharmaceuticals, calPERS ultimately will be forced to raise prescription drug co-pays or raise premiums, shifting the increasingly unaffordable costs onto the individuals who can least afford them.

Mr. Chairman, before I conclude I need to address one important issue. The opponents of this legislation--as you point out, they are limited to the biotech industry--are claiming that those who support your legislation are ignoring the safety threat of bringing biogenerics to the marketplace. I want to be perfectly clear. The safety and health of our members comes first in any decision we make on any health care policy. Therefore, we strongly support providing FDA with full discretion to make the ultimate decision about whether and when any prescription drug product, be it brand or generic, comes to market. Your legislation does just that.

Mr. Chairman, CalPERS is proud to add our support to the growing and diverse list of stakeholders who support your legislation to open the door to biogeneric competition. Thank you for giving us this opportunity.

I would be happy to answer any questions.

[Prepared statement of Ms. Mathur follows:]

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Chairman WAXMAN. Thank you very much for your testimony.

We are going to ask questions after everybody is finished.

Mr. McKibbin?

STATEMENT OF SCOTT MCKIBBIN

Mr. MCKIBBIN. Thank you, Mr. Chairman, and thank you for the opportunity to speak on behalf of Illinois Governor Rod R. Blagojevich in support of establishing a pathway for generic biopharmaceuticals.

I want to applaud Chairman Waxman for his vision, recognizing that escalating cost of biopharmaceuticals to States and consumers is creating an economic burden on Illinoisans and State budgets nationwide. These costs will continue to make it more difficult to balance cost control and access for patients to affordable, life-saving biopharmaceuticals, both in Illinois and in the Nation as a whole.

Further, I would like to recognize Illinois Congressman Emmanuel for his cosponsorship of H.R. 1038, the Access to Life-Savings Medicine Act, and for supporting these important measures.

In my present role as a Special Advocate for

Prescription Drugs, I have functional accountability for overseeing prescription drug spending for the State of Illinois. I am also a two-time kidney cancer survivor, and can speak personally from experience on both the value and the cost of therapies that treat such dreaded diseases as cancer.

I want to make it clear that I have a dual role as Special Advocate. The State of Illinois, as every State, has a responsibility to ensure that prescription drug pharmaceuticals available to consumers are safe and effective, so I would like to dispense with the issue of safety as a given for the discussion of generic legislation.

While some in this debate are seeking to obscure the real issue with inflammatory rhetoric about the potential lack of safety of generic biopharmaceuticals, it is my position that this legislation authorizes FDA to take those scientifically sound steps that are appropriate to ensure the safety of generic biopharmaceuticals.

I want to focus the bulk of my testimony on the reality of biopharmaceutical costs and the value of generic competition in this arena.

Illinois is a partner with the Federal Government in providing and paying for prescription drugs. We are also responsible for providing and nurturing a sound economy in our State, one that does not allow health care costs to

bankrupt our State or to negatively impact employers or the overall business climate of our State. To this end, Governor Blagojevich has introduced a comprehensive program to expand coverage to the 1.4 million uninsured between the ages of 19 and 64, and to offer relief to many of our residents who struggle every day to pay for health care costs covered under the existing insurance plans.

There is some debate as to whether the annual increase of the cost of biopharmaceuticals is 15, 17, or 20 percent, but the difference is, in fact, not material. If, as I believe and my data will show, these expenditures for products are rising at an average of slightly larger than 15 percent annually, then within five years what Illinois spends on these drugs today will double. That would have a dramatic negative effect. We would not be able to afford these medications.

Many States probably don't realize the depth of what they are spending now on biopharmaceuticals. According to IMS, biopharmaceutical sales in 2006 grew to $40.3 billion. While the spending has escalated, a debate over potential for generic biopharmaceuticals has spanned four FDA Commissioners, all with a variety of prioritization on how to establish a biopharmaceutical generic approval process.

States need more than continued discussion on this issue. We need action. Chairman Waxman's bill is a great

first step in actually getting us on the road to creating a framework to permit generic competition and the savings it will create.

To understand the breadth and impact of spending on biopharmaceuticals for Illinois, we examined the leading products and what the State of Illinois spends on these products. The results were staggering.

For our 227,500 member employee retiree group, the State of Illinois spent $33.2 million on a select list of approximately 100 biopharmaceuticals during the fiscal year that just ended July 2006. With that trend, this represents over 12 percent of our entire cost for drugs, and is growing at an astronomical rate both on the price and the utilization side of the ledger. The ingredient cost increase was 49.9 percent, and the plan cost per member was 50.3 percent.

The number of prescriptions for this select list of biopharmaceuticals also rose significantly, a nearly 29 percent increase. For programs administered under the State Medicaid Agency, we have seen similar cost and utilization increases, but on a much larger scale. For the most recent year in which data is available, the cost of 61 biopharmaceuticals was $1,662,000, paid for under the pharmacy benefit side, and an estimated $75 million paid for under the medical and the part D wrap-around program. The grand total exceeded $200 million a year, without trend.

Now, much has been said about the potential cost savings of generic competition. Opponents to creating a pathway for generic competition argue that the cost savings may be only 10 or 20 percent. But let's look at the worst case scenario, a 10 percent savings. If Illinois was able to reduce its 15 percent, 16 percent annual increase in spending on biopharmaceuticals by even 10 percent, then we not only extend our ability to pay for these drugs, but we also extend our ability to continue, under State programs, to provide increased access to them.

The other issue to consider about savings is this--it appears an obvious one from my perspective, but seems lost in this debate. In the past year, biopharmaceutical expenditures have increased at double digit rates. If we do nothing for the rest of 2007, we will end the year even higher expenditures associated with those biopharmaceuticals. Every day that we delay in creating a pathway for generic competition is a day of potential lost cost savings to States, to taxpayers, and to consumers. We can not afford to wait any longer to begin the savings, even if, as opponents predict, the savings would initially only be modest.

Chairman WAXMAN. Thank you very much, Mr. McKibbin. Are you just about to conclude?

Mr. MCKIBBIN. I have just a few more words, Mr. Chairman.

Chairman WAXMAN. Okay.

Mr. MCKIBBIN. I appreciate it.

I would just like to urge Congress to approve this legislation to authorize the FDA to apply sound scientific regulatory criteria that would give Illinois and other States and every consumer and taxpayer lower biopharmaceutical products and increased access, the result from the cost savings.

Thank you, Mr. Chairman.

[Prepared statement of Mr. McKibbin follows:]

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Chairman WAXMAN. Thank you very much for your testimony.

Dr. Grabowski?

STATEMENT OF HENRY GRABOWSKI

Mr. GRABOWSKI. Thank you, Mr. Chairman and members of the Committee. I am Henry Grabowski, Professor of Economics at Duke University.

My comments will focus on the differences between generic drugs and follow-on biologics and how these differences affect the expected budgetary savings. I also discuss the importance of data exclusivity for innovation incentives. With my colleagues, I have examined these issues in two recent peer reviewed studies. I will make these studies available for the record, along with my statement.

Based on our analysis, we conclude that the cost of entry will be significantly higher for follow-on biologics than generic drugs. We expect fewer firms will enter, and average prices will decline less for follow-on biologics. Consequently, conservative budgetary scoring is appropriate in terms of expected savings to the Government and to other payers.

Second, in designing a pathway for follow-on biologics it is also very important that Congress balance price

competition and innovation incentives. In this regard, it is important to include in the legislation a data exclusivity period that takes account of the high cost and risk of developing new entities. My statement provides data from a new study that is peer reviewed and co-authored with Joe DiMasi in this regard. The cost of R&D for a representative new biologic is now over $1 billion when one takes account of preclinical and clinical expenditures, the cost of failures, the cost of capital, and process engineering, which is higher for biologics than pharmaceuticals.

So let me now briefly summarize some of the key differences between follow-on biologics and pharmaceuticals that will affect cost savings in scoring procedures.

The first is clinical trial cost. As we have heard earlier today, some clinical trial data is going to be necessary to demonstrate comparable safety and efficacy, at least for the foreseeable future. In the case of European filings, the estimates range from $10 to $40 million for preclinical studies. This contrasts with $1 to $2 million costs for bioequivalents for generic drugs.

Second is development times. Estimates from generic firms indicate development times for a follow-on biologic are likely to range from five to eight years. By comparison, generic drugs seldom require more than a few years to do required tests and gain regulatory approval.

Third is manufacturing cost and risk. The required capital investment in property, plant, and equipment and the cost of manufacture are also likely to be significantly higher for follow-on biologics.

Fourth, there are important differences on the demand side. It is unlikely that most follow-on drugs will be designated as interchangeable by the FDA, at least not for the foreseeable future and without extensive clinical trials. As a result, we expect the physicians will initially be cautious with respect to the substitution of follow-on products. Health care providers and patients are likely to be wary until clinical experience has accumulated and shown that a follow-on product is a satisfactory therapeutic alternative to the original innovator products.

These costs and demand side differences have important implications for entry and price competition. In our research, we find the number of entrants and the priced discounts of a follow-on biologic are highly sensitive to fixed cost. As a consequence, even very large-selling biologics are likely to have only a few entrants. For markets with only one to three entrants, we project price discounts will be in the range of 10 to 25 percent. This is in accordance with European experience to date.

These differences also have important implications for scoring cost savings. In particular, cost saving estimates

based on the experiences of generic drug utilization and pricing are subject to strong upward biases. A correct accounting of this and all other relevant factors would substantially lower the savings estimates in studies such as that by Express Scripts and the PCMA.

A recent analysis by Avalier Health has very different assumptions in some important dimensions, find much lower cost savings.

The remainder of my statement covers R&D costs and innovation incentives. I understand the bills under consideration have no data exclusivity provisions or patent restoration features for innovators. The fact that there is no data exclusivity provision would allow generic firms to challenge innovators' patents from the date of first marketing approval and to enter the market soon thereafter. The resulting uncertainty in IP litigation would have significant negative incentive effects on capital market decisions for private and public biotech firms with pipelines. Many of these firms are entrepreneurial in nature and have few if any profitable products.

The exclusivity period for pharmaceuticals under Hatch-Waxman is five years. R&D costs have increased substantially since Hatch-Waxman was enacted 20 years ago. Five years does not provide enough time for firms to recoup the high cost of discovering and developing a new medicine.

Break-even returns on R&D for the average new drug and biological product now exceed more than a decade.

Since this legislation will essentially define the terms of competition between innovators and imitators for decades to come, it is critical that it maintains strong incentives for R&D investment in new biopharmaceuticals, as well as provide incentives for price competition.

A data exclusivity period of at least ten years in length would recognize the high cost and risk of developing new biological entities and deter patent challengers from occurring and entering until a more mature phase of the product life cycle. This would also preserve incentives for the development of new indications for existing drugs and harmonize United States law with that of the European Union.

Thank you.

[Prepared statement of Mr. Grabowski follows:]

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Chairman WAXMAN. Thank you very much, Dr. Grabowski.

Mr. Houts?

STATEMENT OF JONAH HOUTS

Mr. HOUTS. Good afternoon, Chairman Waxman and fellow Committee members. My name is Jonah Houts. I am a Senior Analyst with Express Scripts. I am pleased to be here today to discuss the issue of biogenerics from the perspective of a leading pharmacy benefit management company. Express Scripts would like to thank the chairman for his leadership in introducing this legislation, which we believe will fundamentally improve health outcomes by giving patients access to lower-cost biological alternatives..

Express Scripts monitors prescription drug trends and expenditures for 1,600 clients, including large self-insured employers, government payers, unions, and health insurance companies. I would like to talk about three basic issues today. First, I would like to speak about the trend of specialty drug spend, especially biologic agents. Second, I would like to describe the tools used by the PBM industry to control the increase in cost of prescription drugs. Third, I would like to describe how we would apply these tools to biogenerics and the potential benefit to patients, plan

sponsors, and the Government.

Spending on pharmaceuticals now represents 11 percent of total health care spend. Within the pharmaceuticals are specialty drugs. These are the most high-priced biologic agents which we are discussing here today.

I brought an exhibit which may demonstrate the increased growth here. In 2006, spending on specialty drugs was $54 billion, representing 20 percent of pharmaceutical spend. The rate for specialty drugs will almost double by 2010 to $99 billion. This rate of increase is the second highest in all of the health care field, exceeded only by diagnostic imaging tests.

In total, Express Scripts manages the pharmacy benefit for over 50 million individuals in this country. Our mission is to make the use of prescription drugs safer and more affordable. To this end, we have developed sophisticated tools, such as formularies, tiered co-payments, step therapies, and drug utilization management programs, just to name a few. These tools promote the most clinically sound and cost effective use of pharmaceuticals.

One of the most potent tools that we have is the promotion of generic medications. These therapies are time tested and thus are clinically effective. They also have well characterized safety profiles. The additional advantage is that they are the most affordable for both patients and

plan sponsors. For these reasons, patients achieve higher compliance rates with these therapies. Utilizing programs like I previously described, our company has an industry leading generic fill rate of 60 percent.

But it is important to recognize that all of our programs for promoting the use of generics or less expensive branded medications are reviewed by our external pharmacy and therapeutics committee. This committee is made up of both specialty and general medicine doctors, and pharmacists who are not employees of Express Scripts. Safety has and always will be of primary concern to Express Scripts.

As we have stated, spend on biologic agents is increasing at an alarming rate. This legislation will allow for a pathway at the FDA for companies to bring to market generic versions of these important medications.

The PBMs have the tools to assist patients in switching to the most cost-effective biogenerics. In fact, our switching tools will be even more effective in this market because of the limited number of patients, the limited number of prescriptions, the limited prescribing community, and the potential for enormous savings. Our plan sponsors will be very motivated to have us pursue each and every savings opportunity.

We are pleased to hear the FDA today not rule out interchangeability in the future, but, regardless, if the FDA

deems a product is interchangeable or just comparable will be quite effective at working with the prescribing physician to aid patients in receiving the most cost-effective and clinically appropriate therapy.

In the realm of branded pharmaceuticals, drugs compete on their research and development and marketing. It would be irrational for branded drugs to compete on price, as they are competing within a finite group of patients, and price reductions would result in reduced revenues for all manufacturers in the class. Generic drugs, however, can only compete on price. Without this extensive research and development, the only way for a generic to capture market share is on price. This price competition benefits payers, plans, and the Government.

This historic legislation would allow patients, payers, physicians, and PBMs to work together to make these wonderful therapies more available, with improved health outcomes and tremendous savings.

[Prepared statement of Mr. Houts follows:]

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Chairman WAXMAN. Thank you very much, Mr. Houts.

I want to thank all of you for your testimony, especially Ms. Brown and Ms. Nathan. Your very moving testimony is what this legislation is all about. When drugs are miracles, but the miracles are too expensive for people, they are not going to be there for them, and that is why we need to figure out a way to hold down costs. Providing generics is certainly, to me, one of the best ways to hold down costs. Others have suggested other ideas, but competition, market forces I think do work and have worked in the past.

Ms. Mathur, I find it stunning that in California spending on biologics or specialty drugs in 2006 was $83.7 million, and that is at a cost of $55 per day, compared to $2 per day for traditional drugs. If those kinds of spending trends are maintained, what will be the impact on CalPERS and your members in the future?

Ms. MATHUR. I think we really are at unsustainable levels, and what we fear is that in the future we will have to shift more of the cost on to the member, either through increase in co-pays or raising premiums. We have already heard stories from some of our members that, as the cost of health care increases overall, they are less and less able to afford health care, even through our program. I would hate to see some of our members drop health care coverage that is

available to them simply because they cannot afford it.

Chairman WAXMAN. Dr. Grabowski asserts that the savings from generic competition in the biologics context will be modest, in the range of 10 to 25 percent. Waft would even those modest savings mean for CalPERS? And let me ask this also of Mr. McKibbin for Illinois.

Ms. MATHUR. I'm sorry, Mr. Chairman. I thought you were directing that to Mr. Grabowski.

Chairman WAXMAN. The 10 to 25 percent savings, Dr. Grabowski says those are modest.

Ms. MATHUR. Yes.

Chairman WAXMAN. What will that mean, however?

Ms. MATHUR. I think it would be extremely significant. I mean, the cost for some members, $300,000 a year, 10 to 15 percent or 10 to 25 percent is a significant savings. So even though on a percentage basis the savings for biotech drugs or biogenerics might be less than for synthetic drugs, it is certainly, on an aggregate total cost basis, it is going to be a very large number.

Chairman WAXMAN. Mr. McKibbin?

Mr. MCKIBBIN. For Illinois, Mr. Chairman, we are talking about $20 to $50 million, depending on when we start it, if we start it this year. And those are numbers that come out of the base, so, as you know, if this trend continues at 15 percent plus, we, too, like California, will reach this point

where it is not sustainable, so we will either have to make those tough choices of trying to pass more costs or to limit access, which is untenable.

Chairman WAXMAN. Thank you.

Mr. Houts, one of the frequent assertions we hear from BIO, the trade association for the brand name biotech drugs, is that when a generic pathway for biologics is established we are not going to see much in the way of savings because generic biologics won't be interchangeable like they are with traditional generic drugs. Obviously, we might disagree on the number of biologics that will end up being interchangeable, but assuming BIO is correct that a high number of biologics will be just comparable instead of interchangeable, what kind of impact will that have on spending on biologics?

Mr. HOUTS. There is still a significant savings opportunity, even if interchangeability is not granted by the FDA. Managed care plans and the PBMs, a recent example would be in the statin market, where there was a high-priced, effective statin, Statin A, and then a lower-priced and still effective Statin B. While they were different chemical entities, we were able to move market share to the cost-effective product.

We were actually able to move 49 percent of the market share where they weren't interchangeable, as you will. And

so there is still a significant opportunity in the area of biologics to move patients to the preferred safe, effective, cost-effective products.

Chairman WAXMAN. Well, you said it would be safe. When therapeutic switches are made, what process is in place to protect patient safety?

Mr. HOUTS. All of those decisions are reviewed by our pharmacy and therapeutics committee that I referred to in my testimony, and this is composed of specialist physicians, and other physicians to ensure that drugs in those classes will have no adverse effects on patients.

Chairman WAXMAN. Thank you very much.

Mr. Danny Davis?

Mr. DAVIS OF ILLINOIS. Thank you very much, Mr. Chairman.

Once again, let me thank you for calling and conducting this hearing. It has, indeed, been informative, and I want to thank all of the witnesses for their testimony. Especially I want to echo the sentiments that you expressed, Mr. Chairman, relative to the impact of the testimony of Ms. Brown and Ms. Nathan, consumers for whom all of us work, and hopefully, as a result of their experiences and their testimony, it heightens the recognition that we must do something, and do it as quickly as possible, to try and make sure that we have available the very best and the most cost

effective medical care that the Country can provide. So I certainly want to again thank both of you for being here and for your testimony.

Mr. McKibbin, let me just commend the Governor for the State of Illinois. When I see the kind of interest that Rod Blagojevich has shown relative to health care, and especially the effort to try and make sure that pharmaceuticals are available to all of our residents at a cost for which they can pay, it makes me proud to live in the State of Illinois and proud to know that he is, indeed, our Governor. Please convey that to him.

Mr. MCKIBBIN. I will.

Mr. DAVIS OF ILLINOIS. If I could direct your attention to the chart located over here, which shows the five largest Medicare Part B drug expenditures in 2005--and you may not be able to see, but listed are all of the medicines listed of biotech drugs that are regulated as biologics. Spending on Epogen, an anemia treatment, alone, was over $1.7 billion, but it was actually even higher than that, because those numbers on the chart do not include spending on the end-stage renal disease, ESRD program. Three of the other drugs are also anemia treatments, and they collectively represent over $2.1 billion in Medicare spending. Remicade, an arthritis medicine, accounted for $541 million.

My question is: are we seeing those same kind of trends

in the State of Illinois? And in terms of State spending, what are the five top biologics in the State of Illinois?

Mr. MCKIBBIN. Well, Congressman, we are seeing those similar type of numbers, and anyone who has a television will recognize those drugs because they are fairly heavily advertised, but those five drugs on your screen, I did a quick analysis and for those we are talking about $23 million a year, a little over $23 million for those five drugs on your particular chart.

For us, I took a look at the top five for just our State employee retiree group, and those top five were Enbrel, Humira, Avonex--which was talked about earlier--Lantus, and Forteo. Those were the top five drugs from a total dollar amount. On a per patient basis they are slightly different, but those five drugs are our top five, and not dissimilar to your chart. In some cases the difference may be because of Medicare and where Medicare may cover, versus an employee group, but we are seeing those similar types of trends.

Mr. DAVIS OF ILLINOIS. I know that all of us throughout the Country moan and groan and talk about the speculation of Medicare and Medicaid and whether or not there are going to be increases or decreases. Many of the hospitals kind of operate on shaky ground every year. They are wondering whether or not they are going to experience severe cuts.

Are they going to have to close departments or, in some

instances, actually go out of business. Should we continue to see the increase in pharmaceutical drug costs, what impact do you think that would have on the hospitals, for example, in the State of Illinois, as well as throughout the Nation?

Mr. MCKIBBIN. Certainly, Congressman, it could be the tipping point, and that is something that we are very concerned about. I know yourself and others in the delegation are concerned, and we would urge that this legislation be passed sooner rather than later. As I said earlier, you know, that trend am the, every day that goes by is a day that is a lost opportunity, and it may be, in fact, a tipping point for hospitals in the Illinois, metro Chicago, and the rest of the United States.

Mr. DAVIS OF ILLINOIS. Mr. Chairman, I see that the light is on, but could I ask Mr. Houts if he could respond to that same question relative to the continued escalation of pharmaceutical costs without relief, how this will affect the Medicare/Medicaid programs, and certainly their impact on our hospital infrastructures?

Mr. HOUTS. It is not really a field of expertise for me as far as government payers. What I can say is that there is an exceptional opportunity for the Government in terms of Part B and end-stage renal disease, especially looking at those top drugs listed there, to save a pronounced amount of money. And so, as you consider this legislation, you may

want to find ways to make Part B and the ESRD program more comparable to the commercially insured market and adopt some of the tools we use to manage trend.

Mr. DAVIS OF ILLINOIS. Well thank you very much.

Mr. Chairman, again, I just simply want to commend you for your insight in introducing this legislation, the leadership that you continue to provide. I have always known of your strong interest in health care. You probably would not remember it, but way back in a different life when I used to come to D.C. to lobby on behalf of the National Association of Community Health Centers, you were always the person that we felt that we could come to you and get some understanding. I mean, Senator Kennedy over in the Senate and Representative Waxman here in the House, you were our guys. I want to thank you again.

Chairman WAXMAN. Thank you. Now you are one of their guys, too. Thank you for your kind comments.

I very much appreciate all of our witnesses in this panel, as in the previous panels.

I would like to ask unanimous consent that all Members have five days to submit additional questions for the record to the witnesses that have appeared before us today.

That concludes our hearing, and our meeting is adjourned. Thank you very much.

[Whereupon, at 1:29 p.m., the committee was adjourned.]

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PAGE 144

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